

## SUMMARY OF CHANGES – Protocol

**For Protocol Amendment to:** A Randomized Phase II Study of Gemcitabine, Cisplatin +/- Veliparib in Patients with Pancreas Adenocarcinoma and a Known BRCA/ PALB2 Mutation (Part I) and a Phase II Single Arm Study of Single-Agent Veliparib in Previously Treated Pancreas Adenocarcinoma (Part II)

**NCI Protocol #:** 8993

**Local Protocol #:** 12-045

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#	Section	Page(s)	Change
1.	N/A	N/A	Formatting and editorial changes were made throughout the protocol document.
2.	N/A	N/A	NCI Version Date has been updated to 10/23/2023 throughout the protocol
3.	5.1.1	<a href="#">38</a>	Added “The Sponsor will no longer be providing Veliparib, and all treatment with veliparib must end by December 31, 2024. Treatment options will be discussed with patients.”
4.	8.1.1	<a href="#">61</a>	Under the “Agent Ordering and Agent Accountability” section, the date for the discontinuation of ABT-888 (veliparib) was updated to December 31, 2024.

**NCI Protocol #: 8993**

**Local Protocol #: IRB #12-045**

**TITLE:** A Randomized Phase II Study of Gemcitabine, Cisplatin +/- Veliparib in Patients with Pancreas Adenocarcinoma and a Known BRCA/ PALB2 Mutation (Part I) and a Phase II Single Arm Study of Single-Agent Veliparib in Previously Treated Pancreas Adenocarcinoma (Part II). (Version Date: 10/23/2023)

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**NCI Supplied Agent(s):** Veliparib (ABT-888, NSC 737664; IND XXXXXXXXXX)

**Commercial Agents:** Gemcitabine, Cisplatin

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Revision/ 3.0	12/02/2015
Revision/ 4.0	05/06/2016
Revision/ 5.0	09/01/2016
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Revision/ 9.0	03/20/2019
Revision/ 10.0	05/07/2022
Revision/ 11.0	06/14/2023
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## STUDY DESIGN

**Title:** A Randomized Phase II Study of Gemcitabine, Cisplatin +/- Veliparib in Patients with Pancreas Adenocarcinoma and a Known BRCA/ PALB2 Mutation (Part I) and a Phase II Single Arm Study of Single-Agent Veliparib in Previously Treated Pancreas Adenocarcinoma (Part II). NCI #8993.

**Sponsor:** National Cancer Institute

### Objectives (Part I):

1. To optimize the dose of veliparib combined with gemcitabine and cisplatin (non-randomized, lead-in portion of Part I).
2. To evaluate the response rate (RECIST) of gemcitabine, cisplatin and veliparib (Arm A) and gemcitabine and cisplatin (Arm B) in BRCA/PALB2 carriers with advanced pancreas adenocarcinoma.
3. To evaluate progression-free survival in study arms A and B.
4. To describe the safety and tolerability of gemcitabine, cisplatin and veliparib and gemcitabine, cisplatin in BRCA/PALB2 carriers with advanced pancreas adenocarcinoma.
5. To determine the disease control rate (CR + PR + SD) and duration of response.
6. To evaluate overall survival in both study arms.
7. Correlative studies (detailed separately in [section 9.1](#)).

### Objectives (Part II):

1. To evaluate the response rate (RECIST criteria) of single-agent veliparib (Arm C) in BRCA/PALB2 carriers with previously treated pancreas adenocarcinoma.
2. To evaluate progression-free survival for single-agent veliparib in BRCA/PALB2 carriers with previously treated pancreas adenocarcinoma.
3. To describe the safety and tolerability of single-agent veliparib in BRCA/PALB2 carriers with carriers with previously treated pancreas adenocarcinoma.
4. To determine the disease control rate (CR + PR + SD) and duration of response.
5. To evaluate overall survival.

### Study Design:

The study involves two clinical trials, Part I and II with three study arms (Arm A, B for Part I and Part II, Arm C).

#### Part I:

**Arm A:** Gemcitabine, Cisplatin, Veliparib (ABT-888)

**Arm B:** Gemcitabine, Cisplatin

#### Part II:

**Arm C:** Veliparib (ABT-888)

**Part I:**

In Part I patients with untreated metastatic pancreas adenocarcinoma with a known germline BRCA 1, 2 or PALB2 mutation will be randomized to one of two study arms: Patients in Arm A will receive gemcitabine, cisplatin and veliparib. Patients in Arm B will receive gemcitabine and cisplatin. The initial group of patients (n= 6-24) enrolled to Part I of the study will not be randomized and will be treated with the 3-drug combination of gemcitabine, cisplatin and veliparib (please see [below](#)).

**Sample size:**

N= 6-24 patients for lead-in, non-randomized portion of Part I (to optimize the veliparib dosing combined with gemcitabine and cisplatin).

Eligibility: For the lead-in, non-randomized portion of Part I may include patients with a known BRCA/PALB2 mutation and patients who potentially may have a BRCA/PALB2 mutation (personal or family history of breast, pancreas, ovary, endometrial, prostate or other likely related malignancy).

N= 32-50 patients (Simon two-stage minimax design per arm). Initially N= 16 patients will be accrued to both Arm A and B. If two or more responders are observed per arm, that arm will be expanded to N= 25.

Eligibility: Restricted to patients with a known BRCA/PALB2 mutation for the randomized portion of Part I.

**Investigational Products:**

Veliparib (ABT-888, NSC 737664).  
Gemcitabine, Cisplatin (both commercially available).

**Regimen (Arm A, Arm B):**

Gemcitabine 600 mg/m<sup>2</sup> IV over 30 minutes +/- 10 minutes day 3 and 10.  
Cisplatin 25 mg/m<sup>2</sup> IVPB over 30 minutes +/- 10 minutes day 3 and 10.  
Both drugs will be dosed on a day 3, 10 (+/- 48 hour) schedule q 3 weeks. For Arm A, veliparib should start on Day 1 and chemotherapy should be administered on days 3 and 10. For Arm B, a separate Day 1 is not required; Day 1 and Day 3 procedures can be combined.  
Veliparib (Arm A) will be dosed orally twice daily on day 1-12 per MTD, q 3 weeks (day 1 can be adjusted +/- 48 hours). The dosing is being determined from an ongoing clinical trial evaluating the safety and dosing of the combination of cisplatin, gemcitabine and ABT-888 (NCT01282333) and a lead-in portion (described below) to Part I of the current study. As of 02/29/12, the planned start dose of veliparib will be 20 mg PO BID (dose level 0).

There will be a small lead-in, non-randomized portion to Part I, where dose levels of veliparib 20 mg po BID (dose level 0), 40 mg po BID (dose level 1) and 80 mg po BID (dose level 2), will be evaluated on a day 1-12 schedule. The doses of gemcitabine 600 mg/m<sup>2</sup> and cisplatin 25 mg/m<sup>2</sup> are fixed. Three-6 patients will be evaluated per dose level starting with 20 mg po BID (dose level 0). If no dose-limiting toxicity (DLT), the dose of veliparib will be increased to 40 mg po BID (dose level 1) and subsequently to 80 mg po BID (dose level 2). If no DLT is observed at the veliparib dose of 80 mg BID day 1-12, then dose level 2A will examine veliparib at 80 mg po BID day 1-21, i.e., continuous dosing of veliparib. Subsequent cohorts will only examine continuous dosing of veliparib: dose level 3 (140mg po BID) and dose level 4 (200mg po BID). Approximately 6-24 patients total will be evaluated in this lead in portion of the study.

If either 2 out of 3 or 2 out of 6 experience a DLT at a given dose level, then the recommended phase II dose for randomization will be one dose level below.

As of 12/13/13, the finalized dosing for the randomized portion of Part I of the study is as follows: Veliparib 80 mg PO BID day 1-12, gemcitabine 600 mg/m<sup>2</sup> and cisplatin 25 mg/m<sup>2</sup>.

**Key Eligibility Criteria:** Stage III or IV pancreas adenocarcinoma  
Confirmed BRCA 1, 2 or PALB2 mutation  
Measurable disease (either local primary or metastatic disease)  
No prior platinum or PARP inhibitor therapy  
ECOG 0-1

**Key Procedures:** RECIST assessment of tumor response (6 weeks).  
Correlative studies from serum, archival and pre and post treatment tumor biopsies.

## **Part II:**

In Part II of this study the efficacy of single-agent veliparib (Arm C) in patients that who have previously received up to two lines of systemic therapy (for either localized or metastatic disease possibly including cisplatin and gemcitabine), and without prior receipt of a PARP inhibitor, will be evaluated.

This part of the study will accrue patients who were enrolled in Arm B (gemcitabine and cisplatin) of Part I and other patients who will be accrued from other sources with a known BRCA 1, 2 or PALB2 mutation and who have had up to two lines of prior systemic therapy including for either localized or metastatic disease. As of 01/16/15, Part II has been closed to accrual.

<b>Sample size:</b>	N= 15-33 patients (Simon two-stage optimal design). If two or more responders are observed in the first 15 patients, then Arm C will be expanded to 33.
<b>Investigational Products:</b>	Veliparib (ABT-888, NSC 737664).
<b>Dosing Regimen (Arm C):</b>	Veliparib (ABT-888) will be dosed orally twice daily on day 1- 28 (day 1 can be adjusted +/- 72 hours) per recommended phase II dose determined from an ongoing clinical trial evaluating the safety and dosing of this combination (NCT00892736). Veliparib dose: 400mg PO BID continuously.
<b>Key Eligibility Criteria:</b>	Stage III or IV previously treated pancreas adenocarcinoma Confirmed BRCA 1, 2 or PALB2 mutation Measurable disease Up to two lines of prior therapy for localized or metastatic disease No prior PARP inhibitor ECOG 0-2
<b>Key Procedures:</b>	RECIST assessment of tumor response (8 weeks). Correlative studies from archival tumor tissue.

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## 1. OBJECTIVES

### 1.1. Primary Objectives

#### Part I:

- To optimize the dose of veliparib combined with fixed doses of gemcitabine and cisplatin in a (non-randomized, lead in portion of Part I).
- To evaluate the response rate (RECIST criteria) of gemcitabine, cisplatin and veliparib (Arm A) and gemcitabine, cisplatin (Arm B) in BRCA and PALB2 mutation carriers with advanced pancreas adenocarcinoma.

#### Part II

- To evaluate the response rate (RECIST criteria) of single-agent veliparib (Arm C) in BRCA and PALB2 carriers with previously treated pancreas adenocarcinoma.

### 1.2. Secondary Objectives

#### Part I:

- To evaluate the progression-free survival in study Arm A and Arm B.
- To describe the safety and tolerability of gemcitabine, cisplatin and veliparib and gemcitabine and cisplatin in BRCA and PALB2 carriers with advanced pancreas adenocarcinoma.
- To determine the disease control rate (CR + PR + SD) and duration of response in study Arm A and Arm B.
- To evaluate overall survival in study Arm A and Arm B.

#### Part II:

- To evaluate progression-free survival for single-agent veliparib in BRCA and PALB2 mutation carriers with previously treated pancreas adenocarcinoma (Arm C).
- To describe the safety and tolerability of single-agent veliparib in BRCA and PALB2 mutation carriers with carriers with previously treated pancreas adenocarcinoma.
- To determine the disease control rate (CR + PR + SD) and duration of response in Arm C.
- To evaluate overall survival in Arm C.

### 1.3 Correlative Science Objectives ([section 9](#))

#### Aims 1-4

1. To determine the genotype of BRCA1, BRCA2 and PALB2-mutated pancreas adenocarcinoma.
2. To assess pre and post therapy biopsies for novel or persistent genetic alterations in genes identified in aim 1.

3. Two parts:
  - a) To quantify levels of PAR in peripheral blood mononuclear cells (PBMCs) and tumor tissues at sequential time points before and following therapy with veliparib.
  - b) To quantify levels of  $\gamma$ H2AX and RAD51 foci in PBMCs and tumor tissue (where available) at sequential time points to assess for formation of double-stranded DNA breaks, stalled/collapsed replication forks and evaluate homologous recombination competence.
4. Exploratory Objectives
  - a) To correlate the results of genotyping with gene expression to provide functional information on mutations identified.
  - b) An exploratory assessment of differential expression of genes involved in DNA repair pathways pre and post treatment to identify candidate genes predictive of response or resistance to therapy for further study in preclinical models of disease.

## 2. BACKGROUND

### 2.1 CTEP-Supplied Investigational Agent

#### 2.1.1 Veliparib (ABT-888)

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 enzymes. The PARP-1 group of NAD<sup>+</sup>-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 <sup>1</sup>.

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 <sup>2</sup>,

hepatocellular carcinoma<sup>3</sup>, cervical carcinoma<sup>4</sup>, colorectal carcinoma<sup>5</sup>, non-Hodgkin's lymphoma<sup>6</sup>, leukemic lymphocytes<sup>7</sup>, and colon adenomatous polyps<sup>8</sup>. 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<sup>+</sup>-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<sup>9-11</sup>. 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<sup>12-14</sup>.

The zinc finger domain of PARP binds to both single- and double-stranded DNA breaks, resulting in increased catalytic activity<sup>12, 14, 15</sup>. Once activated, PARP cleaves NAD<sup>+</sup> 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<sup>+</sup> 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<sup>16</sup>. Consequently, multiple mechanisms to prevent overactivation of PARP exist. First, auto-PAR negatively regulates PARP activity<sup>17</sup>. 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<sup>14, 18</sup>. 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<sup>19, 20</sup>. Also, small molecule inhibitors of

PARP can directly inhibit the repair of double-stranded breaks<sup>9,21</sup>. 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 (ABT-888) 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 [<sup>3</sup>H]-NAD<sup>+</sup> into histone H1, an important physiological substrate of PARP. In assays measuring inhibition of H<sub>2</sub>O<sub>2</sub>-induced poly(ADP-ribosyl)ation in C-41 cervical carcinoma cells, ABT-888 inhibited PARP with an EC<sub>50</sub> value of 2.4 nM. The extent of DNA damage in cells was indicated by  $\gamma$ -H2AX levels. To determine the effect of ABT-888 in combination with cytotoxic agents on DNA damage, the cellular content of  $\gamma$ -H2AX in C-41 cells was assayed by flow cytometry using an anti- $\gamma$ -H2AX antibody. Addition of 1 mM of temozolomide alone resulted in increased numbers of  $\gamma$ -H2AX foci, a result which was further potentiated by ABT-888 in a dose-dependent manner. When cell survival was measured by an AlamarBlue assay, ABT-888 potentiated cytotoxicity in the same concentration range as used in the  $\gamma$ -H2AX assay, demonstrating that ABT-888 potentiates cytotoxicity of temozolomide by delaying DNA repair. ABT-888 achieved a maximal potentiation of approximately 15-fold. ABT-888 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 ABT-888 *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<sup>22</sup>. Alkylating agents such as temozolomide form methyl adducts in DNA and resistance is frequently encountered in the clinic with either the overexpression of O<sup>6</sup>-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<sup>23</sup>.

There are data to suggest that PARP inhibitors have activity against some BRCA-deficient cells in the absence of any DNA damaging agent<sup>24,25</sup>. 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  $\gamma$ -radiation<sup>26, 27</sup>. There is evidence to suggest that PARP inhibitors sensitize cancer cells to radiation, both *in vitro* and *in vivo*<sup>28-30</sup>. Furthermore, a PARP inhibitor in the same class as ABT-888 potentiated radiation in the HCT116 colon carcinoma model. ABT-888 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](#)). ABT-888 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: Preclinical Data for Veliparib (ABT-888) Mediated Potentiation of Chemotherapeutic 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 (ABT-888) 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 ABT-888 doses, either parenteral or PO. Supratherapeutic doses of ABT-888 (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 ABT-888/cisplatin combination study. When administered as a continuous infusion, an ABT-888 C<sub>ss</sub> (plasma concentration at steady-state) of 70 ng/mL was maximally efficacious (area under the curve [AUC]=1.7  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ). 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  $\mu\text{g}\cdot\text{hr}/\text{mL}$ . 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 ABT-888 alone. Two hours after administration, ABT-888 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  $\times$  5) was administered with ABT-888. In another study, PAR formation was measured in tumors treated simultaneously with temozolomide and ABT-888. As in the ABT-888 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 ABT-888 to inhibit both baseline and cytotoxic-induced PARP activity in tumors treated *in vivo* and provide evidence of the ability of ABT-888 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 ABT-888. 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 ABT-888 was evaluated in CD-1 mice, Sprague-Dawley rats, beagle dogs and cynomolgus monkeys. The non-clinical PK profile of ABT-888 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. ABT-888 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]ABT-888 was rapidly absorbed and cleared primarily in the urine as intact parent drug. A-925088 (M8), a lactam derivative and the major product of ABT-888 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  $\mu$ M) for ABT-888 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 ABT-888 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, ABT-888 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. ABT-888 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 ABT-888 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<sup>31</sup>, 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 ABT-888 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<sub>24</sub> of 3  $\mu\text{g}\cdot\text{hr/mL}$  at steady state.

ABT-888 was tested in receptor-binding, CNS/neurobehavioral, cardiovascular, cardiac electrophysiological and gastrointestinal assays. In 74 receptor-binding assays at a concentration of 10  $\mu\text{M}$  (2.4  $\mu\text{g/mL}$ ), ABT-888 displaced control-specific binding at the human H<sub>1</sub> (61%), the human 5-HT<sub>1A</sub> (91%), and the human 5-HT<sub>7</sub> (84%) sites only, with IC<sub>50</sub> values of 1.2-5.3  $\mu\text{M}$ .

ABT-888 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 ABT-888 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 ABT-888 300 mg/kg IP, protection against seizures was not provided by pretreatment with either valproic acid (300 mg/kg IP, 15 min prior to ABT-888) or diphenylhydantoin (75 mg/kg IP, 100 min prior to ABT-888). In a 2-week toxicology study, seizures were also noted in dogs treated with ABT-888 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  $\mu\text{g/mL}$  (26-fold the predicted clinical C<sub>max</sub> of 0.21  $\mu\text{g/mL}$ ).

In the anesthetized dog, ABT-888 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  $4.45 \pm 0.13 \mu\text{g/mL}$  (21-fold the predicted clinical  $C_{max}$  of  $0.21 \mu\text{g/mL}$ ). As mean plasma concentrations increased to  $12.96 \pm 0.92 \mu\text{g/mL}$  (62-fold), ABT-888 produced a modest reduction in mean arterial pressure ( $-16 \pm 5\%$  below baseline) and systemic vascular resistance ( $-10 \pm 7\%$  below baseline).

ABT-888 blocked hERG current with an  $IC_{50}$  value of  $57.6 \pm 1.7 \mu\text{g/mL}$  ( $236 \pm 7 \mu\text{M}$ ), a value 278-fold higher than the predicted clinical  $C_{max}$ . The M8 metabolite of ABT-888 (A-925088) minimally affected hERG at the highest concentration tested ( $81.5 \mu\text{g/mL}$ ). While no effect on repolarization (*in vitro* action potential duration measures) was noted at the lowest measured concentration of ABT-888 ( $0.42 \mu\text{g/mL}$ , 2-fold higher than the predicted clinical  $C_{max}$ ), ABT-888 prolonged the action potential duration at the intermediate and highest measured concentrations (4.8% and 18.6% prolongation at  $4.22 \pm 0.02$  and  $39.49 \pm 0.70 \mu\text{g/mL}$  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 ( $15 \pm 3\%$  above baseline [QTcV] at  $12.96 \pm 0.92 \mu\text{g/mL}$ ). 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 ABT-888 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  $3.80 \pm 0.11 \mu\text{g/mL}$ , 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  $6.61 \pm 0.26 \mu\text{g/mL}$ , a value 31-fold greater than predicted  $C_{max}$ ). Parenteral (subcutaneous) dosing of ABT-888 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. ABT-888 had no significant effect on gastrointestinal transit up to 100 mg/kg (resulting in a mean plasma concentration of  $1.63 \pm 0.14 \mu\text{g/mL}$ , a value 7-fold greater than the predicted clinical  $C_{max}$ ).

ABT-888 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 ABT-888 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 ABT-888 than the estimated therapeutic value. Exacerbation of cisplatin-associated toxicity was limited to rats that received ABT-888 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. ABT-888 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<sup>2</sup>. 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 (Kummar *et al.*, 2009). 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 ABT-888 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 ABT-888. 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 ABT-888 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.

## 2.2 Gemcitabine, Cisplatin

Please see [section 2.3](#) below regarding the combination of gemcitabine and cisplatin in the treatment of pancreas adenocarcinoma.

## 2.3 Pancreas Adenocarcinoma and BRCA Mutations

Pancreas adenocarcinoma is arguably one of the most challenging of human malignancies and is characterized clinically by late presentation with advanced symptomatic disease and moderate to high treatment resistance. The high case fatality rate, with approximately 43,140 new diagnoses anticipated in the US and almost 36,800 deaths in 2010<sup>32</sup>, illustrate these challenges. These observations are underscored at a molecular level by the genetic complexity of pancreatic cancer with several key oncogenes (K-ras) and tumor suppressor genes (SMAD4/DPC4, p16/INK4A, p53) affected, and the multiplicity of key signaling pathways that are aberrant<sup>33, 34</sup>. There have been major improvements in the understanding of the fundamentals of the

molecular pathogenesis and genetics of pancreas adenocarcinoma that provide new therapeutic insights and the tangible hope is that some of these new opportunities will translate into meaningful improvement in outcomes for this disease.

Progress in clinical therapeutics has been modest and incremental with current standards of care for advanced disease including, gemcitabine or gemcitabine-based combinations with erlotinib or arguably platinum analogs or fluoropyrimidines<sup>35-37</sup>. Pancreatic adenocarcinoma is associated with several single gene mutations that predispose to the development of this malignancy. In particular germ line BRCA 2 and 1 mutations incur an increased risk of developing pancreas cancer estimated to be in the 2.5- 3.5 fold higher than the background population<sup>38-40</sup>. Certain subgroups of patients with pancreatic cancer, e.g. Jewish and of Ashkenazi background, may harbor an even higher risk of carrying a BRCA mutation<sup>41</sup>. Stated another way, up to 5-7% of patients with pancreas adenocarcinoma may harbor a BRCA mutation, particularly BRCA-2<sup>42</sup>.

PALB2 (partner and localizer to BRCA2) mutations occur in a small fraction of patients with pancreas adenocarcinoma<sup>43</sup>. PALB2 has been identified as a susceptibility gene for both breast and pancreatic cancer. Truncating PALB2 mutations were identified in 3 out of 96 American patients with familial pancreas adenocarcinoma. A further 3 truncating PALB2 mutations were identified in a European study of 81 patients with familial pancreas adenocarcinoma, all of whom were confirmed as BRCA 1, 2 mutation negative<sup>44</sup>. All 3 of these patients also had a family history of breast cancer.

The PALB2 protein stabilizes the BRCA 2 protein and anchors it to the nucleus, allowing it to carry out its DNA repair function. More recently, PALB2 has been shown to associate with the BRCA 1 protein, providing a linkage between BRCA 1 and 2 in homologous recombination repair of double-stranded DNA breaks<sup>45</sup>.

In patients with familial pancreatic cancer the frequency of BRCA 1 or 2 mutation carriers is estimated at 11-17%<sup>46, 47</sup>. This figure however may underestimate the true frequency of mutations due to the low numbers of pancreatic cancer patients who proceed to germline testing for BRCA 1, 2 mutations in clinical practice. The increased risk of malignancy in BRCA 1, 2 mutation carriers occurs due to the critical involvement of functional BRCA 1 and 2 in repair of double-stranded DNA breaks by homologous recombination. Preclinical data has demonstrated hypersensitivity of BRCA 2 deficient pancreatic cell lines to DNA cross-linking agents mitomycin and cisplatin<sup>48</sup> and more recently to the novel agents, poly (ADP-ribose) polymerases (PARP) inhibitors<sup>49</sup>. Several anecdotal clinical reports also indicate increased sensitivity to DNA damaging agents in patients with PAC arising on a background of known BRCA 1, 2 germline mutation<sup>50</sup>. This observation of increased sensitivity to therapies targeting the defective DNA repair pathway has been well described previously in patients with BRCA 1, 2 associated breast and ovarian cancers.

### **Therapy of Advanced (Inoperable) Pancreatic Adenocarcinoma**

There are several standard options for treating advanced pancreatic adenocarcinoma, including gemcitabine monotherapy<sup>35</sup>, gemcitabine and erlotinib<sup>36</sup>, gemcitabine and

capecitabine<sup>51</sup> or gemcitabine and a platinum-based option<sup>37, 52</sup>. The response rate to single-agent gemcitabine is between 5 and 10% and results in a median survival of 5-6 months and a 1-year survival of 18%<sup>16</sup>. Combination chemotherapy regimens with platinum agents or with capecitabine enhance response rates, improve time to progression and clinical benefit over single-agent gemcitabine in randomized trials. An overall survival benefit has been difficult to demonstrate for cytotoxic combinations and has been observed only for gemcitabine and capecitabine in preliminary assessment. Moore, et al<sup>36</sup>, presented the results of a randomized phase III trial of gemcitabine and erlotinib compared to gemcitabine alone and reported a small overall survival advantage for the combination, 6.4 vs 5.9 months, with no improvement in response rate and minimal improvement in tumor control rates (CR + PR + SD) over single agent gemcitabine. It is unclear how clinically meaningful these results are, nonetheless, erlotinib has recently been approved in the US and Europe for the treatment of advanced pancreas cancer in combination with gemcitabine.

### **Gemcitabine, Platinum and Newer Combinations**

The combination of gemcitabine and oxaliplatin has been shown to produce significant response rates in patients with advanced pancreatic adenocarcinoma. In a recent GERCOR/GISCAD study the median survival of patients with locally advanced disease treated with gemcitabine/oxaliplatin was 25 months and 10% of patients (3/32) were alive at three years<sup>53</sup>. The overall survival in this phase III trial was 9.0 months for gemcitabine and oxaliplatin versus 7.1 months for gemcitabine ( $p=0.13$ ), constituting the second best overall survival ever reported in any phase III trial in pancreas cancer. The ECOG co-operative group recently reported the final results of a three-arm randomized phase III trial, comparing gemcitabine dosed conventionally over 30 minutes against gemcitabine administered as a fixed dose rate infusion compared to gemcitabine and oxaliplatin<sup>54</sup>. The latter two combinations resulted in approximately a one month difference in median survival over single-agent gemcitabine (6 vs 5 months), which was not statistically significant. Of note is that 88% of these patients had metastatic disease compared to the higher proportion of patients with earlier stage disease in the GERCOR/GISCAD European study.

Pooled and meta-analysis data support the choice of a gemcitabine/platinum combination in good performance status patients<sup>37, 52</sup>. These data are often cited as the rationale for combination gemcitabine/platinum treatment choices, albeit individual studies have not demonstrated a clear survival advantage for gemcitabine/platinum over single agent gemcitabine.

More recently, Conroy, et al, have reported the final results of the PRODIGE 4/ACCORD 11 randomized phase III trial comparing FOLFIRINOX to gemcitabine<sup>55</sup>. Patients with an ECOG performance status of 0-1 with metastatic untreated pancreas adenocarcinoma (almost 40% in each group were 0), were randomized to either standard dose gemcitabine or FOLFIRINOX (oxaliplatin 85 mg/m<sup>2</sup>, irinotecan 180 mg/m<sup>2</sup>, and leucovorin 400 mg/m<sup>2</sup> on day 1 of a biweekly cycle, followed by a bolus of 400mg/m<sup>2</sup> and a 46-hour continuous 5-FU infusion at 2,400mg/m<sup>2</sup>). Three hundred and forty two patients were enrolled. At a planned

interim analysis after 167 events (death), the data and safety monitoring board closed the study as the primary study endpoint was met. In the FOLFIRINOX arm, the response rate was 31.6% (versus 9.4% for gemcitabine), progression-free survival was 6.4 months (versus 3.3 months), and the median overall survival was 11.1 months versus 6.8 months, HR= 0.57,  $p < 0.0001$ . Grade 3-4 fatigue and gastrointestinal side effects were more common in the FOLFIRINOX arm. Additionally, grade 3-4 neutropenia occurred in 46% of the combination arm versus 19% in gemcitabine-treated patients, and febrile neutropenia rates were 5.4% and 0.6%, respectively, both statistically significant.

For the purposes of this clinical trial, we have not chosen FOLFIRINOX as the cytotoxic backbone for several reasons: (1) the relative superiority/toxicity balance of a two drug vs three drug combination in advanced pancreas adenocarcinoma has not been established, (2) we foresee difficulties combining veliparib (ABT-888), a relatively myelosuppressive drug, with FOLFIRINOX, and (3) we intend to include performance status 2 patients where FOLFIRINOX would not be suitable, (4) in a selected BRCA/PALB2 population the likely key contributors to treatment efficacy are the platinum agent +/- the PARP inhibitor. Hence the standard regimen that we will use will be gemcitabine and cisplatin.

### **PARP Inhibitors**

PARP are a family of enzymes, two of which, PARP1 and 2, are key components of the DNA repair mechanism for cells with single-strand breaks and nucleoside base damage<sup>56</sup>. PARP inhibition is achieved by competitive blockade of the catalytic domain of the PARP enzyme, preventing binding of the NAD<sup>+</sup> substrate, and so production of ADP-ribose. This approach has particular application in tumours with pre-existing defects in homologous recombination, such as BRCA 1 or 2 deficient cells<sup>57</sup>. Inhibition of PARP in these cells leads to transformation of background single-strand breaks into double-strand breaks (DSB), which are cytotoxic in cells which are unable to repair DSBs by homologous repair. Preclinical data in the pancreatic adenocarcinoma cell line, BRCA2 mutated CaPan-1, demonstrates single agent activity for the PARPi, KU-0058684 and for combinations with cytotoxic agents<sup>58, 59</sup>.

This effect of synthetic lethality provides the therapeutic rationale for development of PARP inhibitors for BRCA 1 or 2 mutation associated malignancies, with considerable efficacy shown to date in phase I and II clinical trials of BRCA-mutant breast and ovarian cancer<sup>60, 61</sup>.

## **2.4 Study Rationale**

BRCA proteins and other DNA repair mechanisms, including base excision repair and direct reversal of DNA damage, function in a complementary manner. In BRCA and PALB2-mutated pancreas adenocarcinoma, inhibition of complementary repair function should increase the sensitivity of cancer cells to killing by both platinum related therapy and the PARP inhibitor veliparib (ABT-888). Gemcitabine and cisplatin is an established regimen for treating stage III or stage IV pancreas adenocarcinoma. The regimen is of particular relevance in BRCA-related pancreas

adenocarcinoma.

This study will evaluate a series of important questions in BRCA and PALB2-mutated pancreas adenocarcinoma and will determine the following in this specific patient population:

- Evaluate the activity of gemcitabine and cisplatin (Arm B).
- Evaluate the addition of the PARP inhibitor, veliparib, combined with gemcitabine and cisplatin (Arm A).
- Evaluate the efficacy of single-agent veliparib (Arm C) in previously treated BRCA and PALB2-mutated pancreas adenocarcinoma.

We believe that evaluating PARP inhibition in a narrow subset of patients with pancreatic adenocarcinoma that harbor germline BRCA 1, 2 or a PALB2 mutation with a combination approach of PARP inhibitor (PARPi) and DNA damaging agent or single-agent PARPi is important and will establish a ‘proof of principle’ that a defined subset of patients with pancreatic cancer can experience major therapeutic benefit from targeted therapy. This would also support using other ‘targeted’ approaches in other subgroups of pancreas cancer patients.

#### **Dosing of Gemcitabine/Cisplatin and Veliparib in Pancreas Cancer:**

The combination of gemcitabine and cisplatin, as noted in prior sections, has been evaluated at various dose and schedules in sporadic pancreas adenocarcinoma<sup>62-64</sup>. No clearly superior dosing schedule has been identified. In advanced biliary cancers (cholangiocarcinoma, gallbladder, ampullary) Valle et al, conducted a randomized phase III trial with gemcitabine and cisplatin compared to gemcitabine alone and observed an improvement in response rate, progression-free and overall survival for the combination arm<sup>65</sup>. The dosing in the experimental arm was gemcitabine 1000 mg/m<sup>2</sup> on day 1 and 8 and cisplatin 25 mg/m<sup>2</sup> on day 1 and 8 every 3 weeks. In patients with BRCA and PALB2 mutated pancreas cancer, in view of the putated sensitivity of these tumors to platinum-based therapy, high doses of platinum and gemcitabine are likely not needed for activity.

A CTEP-sponsored ongoing phase I trial, NCT01282333 is evaluating the dose and schedule of gemcitabine and cisplatin with veliparib in patients with sporadic pancreas, biliary, bladder and non-small cell lung cancer. The dosing schedule in that study is as follows: Veliparib PO BID day 1- 12, cisplatin (75 mg/m<sup>2</sup>) and gemcitabine (750 mg/m<sup>2</sup>) day 3, and gemcitabine (750 mg/m<sup>2</sup>), day 10, q 3 weeks. The dose levels of veliparib are 10 mg PO BID (level 1) and 20 mg PO BID (level 2), 40 mg PO BID (level 3) and 80 mg PO BID (level 4). As of 02/2012, this study is ongoing and is currently accruing at the second dose level of veliparib (20 mg PO BID). For dose level 1 no DLT's were observed, but some dose reductions were needed in later cycles. In dose level 2, both activity and myelosuppression has been observed and the cohort has been expanded to 6 patients in view of one DLT (personal communication with PI, Dr. Leonard Appelman UPMC, 02/12, CTEP 02/27/12). Study update 04-15-2013: Dose level 2 (veliparib 20 mg PO BID day 1-12) exceeded tolerability in view of significant myelosuppression and thus the 3-drug

combination at these cytotoxic doses adjudicated as most likely not feasible for further study (personal communication).

In discussion with Dr. Alice Chen and colleagues at CTEP on 02/03/12 a collective decision was made to perform a lead-in non-randomized portion to evaluate higher dose levels of veliparib (20 mg po BID, 40 mg po BID, 80 mg po BID) with lower doses of gemcitabine and cisplatin.

In order to proceed with the current trial we propose to modify the dosing of gemcitabine and cisplatin as follows: (1) to administer gemcitabine at 600 mg/m<sup>2</sup> IV over 30 minutes (+/- 10 minutes) on day 3 and 10; (2) to split the cisplatin dose and administer at 25 mg/m<sup>2</sup> IVPB on day 3 and 10, i.e., at a lower total dose per cycle than employed in the phase I, NCT01282333. The veliparib start dose will be 20 mg PO BID day 1-12 (dose level 0). We will perform a lead-in portion to Part I, non-randomized, where the dose levels of veliparib 20 mg PO BID (dose level 0), 40 mg PO BID (dose level 1) and 80 mg PO BID (dose level 2) will be explored. If the 80 mg PO BID day 1-12 veliparib dose level is cleared, then the following may be assessed: veliparib 80 mg PO BID day 1-21 (i.e., continuous dosing), dose level 2A; 140 mg PO BID day 1-21 continuous dosing (dose level 3) and 200 mg PO BID day 1-21 continuous (dose level 4). The reasons for this are to maximize the dosing of the PARP inhibitor, veliparib, in combination with fixed dosing of gemcitabine and cisplatin. A total of N = 6-24 patients will be included in this part of the study (non-randomized, lead-in Part I).

#### IRB #12-045 study update 04-15-2013

For Part I: 8 patients have been enrolled

Dose level 0 (veliparib 20 mg PO BID day 1-12) N= 3. No DLT. 1 PR.

Dose level 1 (veliparib 40 mg PO BID day 1-12) N= 3. No DLT. 1 PR.

Dose level 2 (veliparib 80 mg PO BID day 1-12) N= 2. No limiting toxicity thus far – ongoing enrolment on this cohort. Too early for response assessment.

Thus far, two ongoing partial responses have been observed in pancreas adenocarcinoma in patients with BRCA mutations on dose level 0 (20 mg PO BID day 1-12) and dose level 1 (40 mg PO BID day 1-12). These data provide reassurance that in this patient population the dosing of cisplatin and gemcitabine is adequate. However, we would like to further optimize the dosing of veliparib and propose to do so by changing the veliparib dosing to continuous dosing (day 1-21) and to add further cohorts to increase the dose of veliparib. The dosing of gemcitabine and cisplatin will remain fixed at 600 mg/m<sup>2</sup> and 25 mg/m<sup>2</sup> respectively.

We have discussed the above with Dr. Alice Chen, CTEP Senior Investigator and Medical Monitor for this study on 04/15/13 who is in agreement with this plan.

For **Part I**: The dosing schedule is as follows for Arm A:

Veliparib 20 mg PO BID day 1-12 (dose level 0), 40 mg PO BID day 1-12 (dose level 1), 80 mg PO BID day 1-12 (dose level 2), 80 mg PO BID day 1-21 continuous (dose level 2A); 140 mg PO BID day 1-21 continuous (dose level 3) and 200 mg PO BID

day 1- 21 continuous (dose level 4).

Gemcitabine 600 mg/m<sup>2</sup> IV over 30 mins (+/- 10 minutes) day 3, 10

Cisplatin 25 mg/m<sup>2</sup> IVPB over 30 mins (+/- 10 minutes) day 3, 10

Each cycle is 3 weeks long. There is a 48 hour treatment window for days 1, 3 and 10. For Arm A, veliparib should start on Day 1 and chemotherapy should be administered on days 3 and 10. For Arm B, a separate Day 1 is not required; Day 1 and Day 3 procedures can be combined.

IRB #12-045 Study Update 12/13/13

Lead-in, non-randomized portion Part I: Seventeen patients have been enrolled of which 9 have had a BRCA mutation. Four dose levels have been assessed (level 0, 1, 2 and 2A). Dose limiting hematologic toxicity was observed in 2 of 6 patients at dose level 2A (grade IV neutropenia/thrombocytopenia). Partial responses have been seen in the BRCA-mutated patients and stable disease in the non-BRCA mutated patients.

The recommended doses for the randomized portion of Part I have been established as follows: Veliparib 80 mg PO BID day 1-12, Gemcitabine 600 mg/m<sup>2</sup> IV day 3 and 10, cisplatin 25 mg/m<sup>2</sup> IVPB day 3 and 10, q 3 weeks.

#### For **Part II:**

The dose of veliparib as a single agent (Arm C) will be determined from an ongoing phase I trial, NCT00892736 (NCI #8282): ABT-888 in Treating Patients with Malignant Solid Tumors That Did Not Respond to Prior Therapy. Eligibility includes a BRCA-related malignancy. Currently the trial is in its 9<sup>th</sup> cohort of dose escalation of 500mg PO BID and is using a continuous dosing plan. At this 500mg BID dose level, one DLT has been identified due to nausea, vomiting and dehydration. The dose level of 400mg PO BID has been expanded to N= 6. One episode of seizure as occurred in the expanded cohort. An ongoing phase II GOG-0280 protocol is evaluating veliparib at 400mg PO BID in previously treated BRCA-germline mutated ovarian cancer. In discussion with Dr. Alice Chen (CTEP) and Dr. Shannon Puhalla, the recommended phase II starting dose for this study (Part II, Arm C) will be increased to veliparib 400mg PO BID (personal communication 12/03/2012). If significant nausea is identified, the dose will be lowered to veliparib 300mg PO BID.

Dosing schedule: Veliparib 400 mg PO BID day 1-28 (continuous). Day 1 can be adjusted +/- 72 hours.

## 2.5 Correlative Studies Background

### Background

Our group at MSK has recently reported a review of clinical features and outcomes of patients treated at MSK for *BRCA 1* and *BRCA2* mutation associated pancreatic cancer<sup>66-6866-68</sup>. In this article, we noted: of 14 patients with BRCA-mutated pancreas adenocarcinoma that 5 of 6 patients treated with platinum-based therapy in a front-line setting for metastatic disease experienced a partial response to therapy and 3 of 4

patients treated with chemotherapy +/- PARP inhibitor also achieved a partial response to this treatment. In addition activity was noted to single-agent PARPi therapy<sup>68</sup>.

The correlative studies and funding for these studies will be supported by a grant from the Lustgarten Consortium for Pancreas Research. There are four major aims which are summarized in [section 9](#).

#### 2.5.1 Immunoassay for poly-ADP-ribosylated (PAR) substrates

Because the product of the PARP enzyme is poly-ADP-ribosylated (PAR) molecules, an immunoassay to quantify the amount of cellular PAR was developed as a clinical biomarker of PARP inhibition. Abbott Laboratories and the NCI-Frederick laboratories developed and cross-validated a quantitative immunoassay for PAR [Kinders, et al.]. The validated assay is a sandwich enzyme chemiluminescence immunoassay employing commercially obtained antibodies to PAR, and pure PAR as a standard. Assay dynamic range is 31 to 2000 pg/mL PAR, with a lower limit of quantitation of approximately 15 pg/mL PAR. The standard curve is linear throughout the range (with an adjusted R<sup>2</sup> typically better than 0.98). The assay uses high, midrange, and low controls produced from the human melanoma line Colo829. Specimen handling was optimized for both PBMCs and tumor needle biopsies (18 ga), and harmonized for use with the same standards and controls. Specimens could be subjected to at least 3 freeze-thaw cycles without a detectable loss of antigen binding. Assay precision was determined at both Abbott and the NCI-Frederick, to be better than 80% (estimated total imprecision at Abbott, 7% or less). Accuracy, as assessed by spike recovery of pure PAR into PBMC lysates, was 100% +/- 20%. Assay dilution linearity was established for the Colo829 controls and tumor lysates, although deviations from linearity are observed in some tumor homogenates, and assay conditions are controlled to compensate for that lack of linearity. The validated assay was used to measure PAR levels in PBMCs of healthy donors, in animal models after administration of a single and multiple dosing of ABT-888, and has been used successfully in real time to measure PAR in PBMCs and tumor biopsies in a phase 0 clinical trial at the NCI (Kummar *et al.*, 2009).

### 3. PATIENT SELECTION

#### 3.1 Eligibility Criteria

- 3.1.1 Male or female patients with cytologically or histologically confirmed locally advanced or metastatic pancreas adenocarcinoma with a BRCA 1 or 2 or PALB2 mutation confirmed by report from Myriad Genetics (USA), Reports from other molecular diagnostic companies can be used to confirm mutations as well. BRCA 1 or 2 or PALB2 mutation can be confirmed locally for all international sites.

For Part I, non-randomized, lead-in portion, patients with a known BRCA 1 or 2 or PALB2 mutation are eligible along with patients who potentially may have a

likelihood of having a BRCA mutation (e.g., personal or family history of breast, pancreas, ovary, endometrial, prostate or other likely related malignancy).

For Part I, randomized portion, a known BRCA 1 or 2 or PALB2 mutation is required.

3.1.2 Eligibility regarding prior therapy:

**For Part I (Arms A, B):**

Patients can have either locally advanced or metastatic pancreas adenocarcinoma for which no prior therapy has been administered for either locally advanced or metastatic disease. Prior adjuvant therapy is permissible if gemcitabine or a fluoropyrimidine was administered with or without radiation and if disease recurrence has been documented at least 6 months after completion of adjuvant therapy.

**For Part II (Arm C):**

Patients can have either locally advanced or metastatic pancreas adenocarcinoma. Up to two prior treatment regimens are permissible (excluding a prior PARP inhibitor) for either localized or metastatic pancreas adenocarcinoma. Prior combined chemotherapy and radiotherapy is permissible provided the patient has measurable disease outside the radiation port. Prior therapy must have been completed at least 3 weeks prior to starting therapy.

3.1.3 Age >18 years. No dosing or adverse event data are currently available on the use of veliparib in patients <18 years of age, therefore children are excluded from this study.

3.1.4 ECOG performance status:

For **Part I** (Arm A, B): 0-1 (Karnofsky > 70%, see [Appendix A](#)).

For **Part II** (Arm C): 0-2 (Karnofsky ≥ 60%, see [Appendix A](#)).

3.1.5 Life expectancy of greater than 3 months.

3.1.6 Patients must have normal organ and marrow function measured within 14 days prior to administration of ABT-888 as defined below:

absolute neutrophil count	≥ 1,500/mcL
hemoglobin	≥ 9.0 g/dl
platelets	≥ 100,000/mcL
total bilirubin	≤ 2 X institutional upper limit of normal

AST(SGOT)/ALT(SGPT) ≤ 2.5 X institutional upper limit of normal  
unless there is evidence of liver metastases in which case the AST  
(SGOT)/ ALT (SGPT) must be ≤ 5 X institutional upper limit of normal

creatinine	≤ 1.5 x ULN
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- 3.1.7 Measurable disease by RECIST criteria.  
For the lead-in, non-randomized portion of **Part I**, either measurable or evaluable disease is acceptable.
- For **Part I**, randomized portion, measurable disease is required.
- 3.1.8 If a woman is of child-bearing potential a negative blood or urine pregnancy test is required. [The effects of veliparib on the developing human fetus are unknown. For this reason and because other therapeutic agents or modalities used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately].
- 3.1.9 Ability to understand and the willingness to sign a written informed consent document.

## 3.2 Exclusion Criteria

- 3.2.1 Patients who have had chemotherapy or radiotherapy within 3 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 3 weeks earlier.
- For **Part I**, prior adjuvant therapy with gemcitabine or a fluoropyrimidine therapy is permitted if completed > 6 months prior to recurrence. No prior PARP inhibitor therapy is allowed.
- For **Part II**, no prior PARP inhibitor therapy is permitted and up to two prior treatment regimens are permitted as follows: 1 adjuvant and 1 metastatic; 1 locally advanced and 1 metastatic; or 2 metastatic, or a variation thereof.
- 3.2.2 Patients may not be receiving any other investigational agents.
- 3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to veliparib or other agents used in study.
- 3.2.4 For **Part I**: patients with known contraindications to platinum agents are excluded.
- 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 Pregnant women are excluded from this study because veliparib is a PARP inhibitor with the potential for teratogenic or abortifacient effects. Because there

is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with 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.

- 3.2.7 Patients with a known active infection, e.g., hepatitis B virus, hepatitis C virus. HIV positive patients who are otherwise well and who do not have evidence of significant immune compromise are eligible.
- 3.2.8 Patients with active seizure or history of seizure are not eligible.
- 3.2.9 Patients with uncontrolled CNS metastasis are not eligible. Patients with CNS metastases are to be stable for >3 months after treatment and off steroid treatment prior to study enrollment.
- 3.2.10 Patients with prior malignancy successfully treated who are currently stable and on no active treatment are eligible.
- 3.2.11 Patients who are unable to swallow pills/capsules are ineligible.
- 3.2.12 Patients with treatment-related AML (t-AML)/MDS or with features suggestive of AML/MDS are ineligible.
- 3.2.13 Patients with prior allogeneic bone marrow transplant or double umbilical cord blood transplantation are ineligible.

### **3.3 Inclusion of Women and Minorities**

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

### **3.4 Recruitment Plan**

This study will be available to all patients seen at Memorial Hospital and each participating data collection site who meet the eligibility criteria outlined in [section 3](#).

Memorial Hospital and the collaborating centers are referral centers for pancreatic cancer. In addition, the study will be placed on the MSK Website as well as the NCI Clinical Trials website and the websites for the other participating centers. Patients will be identified in medical oncology clinics for treatment of their disease. Patients will be identified for potential inclusion in these trials based on either (1) history of a known BRCA 1, 2 or PALB2 mutation, or (2) a strong family or personal history of relevant malignancy (e.g., breast, ovary, prostate, endometrial cancer, etc), suggesting that there is reasonable likelihood of having an underlying mutation. The BRCAPRO computer program may also be utilized to identify patients who are more likely to harbor a mutation and thus suited for genetic testing. The BRCAPRO model is a statistical modeling program that predicts the likelihood of having a deleterious BRCA 1 or 2 gene mutation.

These patients will be promptly evaluated at MSK by the Clinical Genetics service

for testing and a similar approach will be undertaken in US collaborating institutions. If testing yields a positive deleterious mutation confirmed by Myriad Genetics or local evaluation protocols, these patients will be eligible for potential inclusion in the study. The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. The registration procedure will be conducted as described in [section 4](#). Patients will not receive payment for their participation on this study. The proposed study population is provided in the table [below](#).

Accrual Targets				
Ethnic Category	Sex/Gender			
	Females		Males	Total
Hispanic or Latino	11	+	11	= 22
Not Hispanic or Latino	42	+	43	= 85
<b>Ethnic Category: Total of all subjects</b>	53 (A1)	+	54 (B1)	= 107 (C1)
Racial Category				
American Indian or Alaskan Native	0	+	0	= 0
Asian	5	+	5	= 10
Black or African American	6	+	6	= 12
Native Hawaiian/Pacific Islander	1	+	1	= 2
White	41	+	42	= 83
<b>Racial Category: Total of all subjects</b>	53 (A2)	+	54 (B2)	= 107 (C2)

#### 4. REGISTRATION PROCEDURES/ RANDOMIZATION PROCEDURES

##### 4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (<https://ctepcore.nci.nih.gov/iame>). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (<https://ctepcore.nci.nih.gov/rcr>). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓	
HSP/GCP training	✓	✓	✓	
Agent Shipment Form (if applicable)	✓			
CV (optional)	✓	✓	✓	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP websites and applications. Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR *Help Desk* by email at [RCRHelpDesk@nih.gov](mailto:RCRHelpDesk@nih.gov).

## 4.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Patient Selection, [section 3](#).

Obtain written informed consent by following procedures defined in section entitled [Informed Consent Procedures](#).

During the registration process, registering individuals will be required to complete a protocol-specific eligibility checklist. The individual signing the Eligibility Checklist is confirming that the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

### 4.2.1 For Participating Sites:

Central registration for this study will take place at MSK

To complete registration and enroll a participant from another institution, the participating site must contact the MSK study coordinator to notify him/her of the participant registration.

The following documents must be sent to the MSK study coordinator for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSK eligibility checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (laboratory results, BRCA1 or BRCA2 or PALB2 genetics report, pathology report, radiology reports, MD notes, physical examination sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the MSK study coordinator will conduct an interim review of all documents. If the eligibility checklist is not complete or source documentation is missing, the participating site will be responsible for sending the completed registration documents within 30 days of the consent.

If the external registration submission is complete, the participating site IRB has granted approval for the protocol, and the participating site is in good standing, the MSK study coordinator will register the patient.

Once the participant is registered, the participant will be assigned a protocol participant number. This number will be relayed back to study staff at the registering participating site via e-mail and will serve as the enrollment confirmation. The number is unique to the participant and must be written on all data and correspondence for the participant.

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

### 4.3 Patient Randomization

The initial portion of Part I of the study will be non-randomized. A total of 6-24 patients will be evaluated at 2-6 different dose levels of veliparib (20 mg PO BID, 40 mg PO BID, 80 mg PO BID, days 1-12, 80 mg PO BID, days 1-21, 140 mg PO BID, days 1-21, 200 mg PO BID days 1-21). The starting dose for veliparib is 20 mg PO BID (dose level 0).

For the initial non-randomized portion of Part I, patients with a known BRCA or PALB2 mutation or patients potentially likely to have a mutation, are eligible (see section 3.1.1).

Subsequently for **Part I** of the study when the veliparib dosing has been finalized, eligible patients will be enrolled to either Arm A (gemcitabine, cisplatin and veliparib) or Arm B (gemcitabine, cisplatin). Randomization will be accomplished by the method of random permuted block. There are no planned stratification factors. The Arm assignment (A or B) will be emailed back to the participating site with the

protocol participation number.

For **Part II** of the study, eligible patients will be enrolled to Arm C, single-agent veliparib. There is no randomization for this part of the study.

For patients who have previously been enrolled in Arm B of Part I, they may be eligible, on progression of disease, for enrollment into Part II of the study. If so, they are required to meet all eligibility requirements for Part II and sign a separate consent to proceed with Part II (Arm C, single-agent veliparib). Patients will also be accrued outside of Part I of the study, provided all eligibility criteria outlined in [Section 3](#) are met.

For baseline study evaluations please see study calendar, [Section 10](#).

## 5. TREATMENT PLAN

### 5.1 Treatment Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in [Section 7](#). Appropriate dose modifications for cisplatin, gemcitabine and veliparib 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 initial 6-24 patients enrolled in the study will not be randomized and will be part of a lead-in portion to Part I. This group of patients can have either measurable or evaluable disease and have a known or possible BRCA or PALB2 mutation. Gemcitabine and cisplatin will be dosed as [below](#) and veliparib will be dosed starting at 20 mg po BID day 1-12 (dose level 0), with dose levels of 40 mg po BID day 1-12 (dose level 1) and 80 mg po BID day 1-12 (dose level 2), 80 mg po BID day 1-21 (continuous dosing; dose level 2A), 140 mg po BID day 1-21 (dose level 3) and 200 mg po BID day 1- 21 (dose level 4). The purpose of this non-randomized lead-in portion to Part I is to optimize the dosing of veliparib with the combination of gemcitabine and cisplatin.

#### Dose Levels for Lead-In Portion, Non-Randomized, Part I

Part I: Dosing Schedule Arm A and Arm B
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Dose Level	Veliparib Dose (mg day)	Gemcitabine (mg/m <sup>2</sup> )	Cisplatin (mg/m <sup>2</sup> )	N
0 (start level)	20 mg po BID day 1-12	600	25	3-6 patients
1	40 mg po BID day 1-12	600	25	3-6 patients
2	80 mg po BID day 1-12	600	25	3-6 patients
2A	80 mg po BID day 1-21	600	25	3-6 patients
3	140 mg po BID day 1-21	600	25	3-6 patients
4	200 mg po BID day 1-21	600	25	3-6 patients
<p>Note that veliparib doses are “flat” and <u>not</u> calculated based on weight or BSA.</p> <p>The final dose level for the randomized portion of Part I will be determined from the lead-in dose-evaluation from the non-randomized portion of Part I</p>				

After the dosing of veliparib has been finalized, patients eligible for **Part I** of the study will be randomized to **Arm A or Arm B**. All patients included in the randomized part of the study must have measurable disease and a BRCA or PALB2 mutation.

**Patients participating in the non-randomized, lead-in portion of Part I, will not undergo research tumor biopsies or have serum/blood samples obtained for correlative studies. Archival tumor specimens will be obtained for these patients.**

For all of Part I, the cycle length is 21 days and patients will be evaluated for response every 6 weeks. After 6 months on study, scans can be done every 9 weeks. After 18 months on study, scans can be done every 12 weeks. At the beginning of year 4, scans can be done every 16 weeks +/- 8 weeks.

As of 12/13/13, the dosing for Part I, randomized portion of the study, has been finalized. Dose level 2 of veliparib, 80 mg PO BID day 1-12, q 3 weeks will be utilized. The lead-in, non-randomized portion of Part I has been closed and all patients accrued to Part I of the study after 12/13/13, will be accrued to the randomized portion of the trial.

**Arm A:** Gemcitabine 600 mg/m<sup>2</sup> IVPB day 3 and 10, Cisplatin 25 mg/m<sup>2</sup> IVPB day 3, 10, and Veliparib 80 mg PO BID day 1-12, all q 3 weeks.

**Arm B:** Gemcitabine 600 mg/m<sup>2</sup> IVPB day 3 and 10, Cisplatin 25 mg/m<sup>2</sup> IVPB day 3, 10, all q 3 weeks.

There is a +/- 48 hour treatment window around days 1, 3, and 10 for the lead-in portion of Part I as well the randomized Arms A and B. For Arm A, veliparib should start on Day 1 and chemotherapy should be administered on days 3 and 10. For Arm B, a separate Day 1 is not required; Day 1 and Day 3 procedures can be combined.

Patients eligible for **Part II** of the study will be allocated to **Arm C**.  
The cycle length is 28 days and patients will be evaluated for response every 8 weeks.

There is a +/- 72 hour treatment window around day 1 for Arm C.

In addition, patients are permitted to have a new cycle of therapy delayed up to 7 days for major life events (i.e. serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a deviation. Documentation to justify this delay should be provided.

**Arm C:** Veliparib 400 mg PO BID day 1-28 continuously.

<b>Part II: Dosing Schedule Arm C (Veliparib only)</b>			
<b>Dose Level</b>	<b>Dose Levels*</b>		
	<b>Veliparib (mg)</b>	<b>N/A</b>	<b>N/A</b>
Level -3	100 mg PO BID		
Level -2	200 mg PO BID		
Level -1	300 mg PO BID		
Level 0	400 mg PO BID		
Note that veliparib doses are “flat” and <b>not</b> calculated based on weight or BSA.			

#### 5.1.1 Veliparib (ABT-888)

Veliparib will be administered orally without regards to meals. Missed veliparib doses should not be made up. Veliparib is supplied as 20 mg, 40 mg, 50 mg, and 100 mg capsules. The veliparib capsules should not be opened. All patients who are receiving veliparib will be provided with a pill diary. Missed doses should be recorded on the pill diary but will not be considered violations of the protocol.

For **Arm A** (Gemcitabine, cisplatin and veliparib), veliparib will be dosed orally twice daily starting at 80 mg PO BID for days 1-12, q 3 weeks. Each dosing cycle is 3 weeks +/- 48 hours. Day 1 dosing should start in the AM however, PM start is acceptable due to appointment time scheduling.

For **Arm C** (Veliparib), veliparib will be dosed orally twice-daily starting at 400 mg PO BID for days 1-28 continuously. Each dosing cycle is 4 weeks +/- 72 hours.

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.

The Sponsor will no longer be providing Veliparib, and all treatment with veliparib must end by December 31, 2024. Treatment options will be discussed with patients.

#### 5.1.2 Gemcitabine, Cisplatin

Gemcitabine will be administered as an intravenous infusion over 30 minutes +/- 10 minutes. Cisplatin will be administered as an intravenous infusion over 30 minutes +/- 10 minutes. Gemcitabine will always be administered first.

Gemcitabine 600 mg/m<sup>2</sup> IVPB over 30 minutes +/- 10 minutes, on day 3 and 10 +/- 48 hours, followed by a rest week.

Cisplatin 25 mg/m<sup>2</sup> IVPB over 30 minutes +/- 10 minutes, on day 3 and 10 +/- 48 hours, followed by a rest week.

Each treatment cycle is 3 weeks. For Arm A, veliparib should ideally start on Day 1 and chemotherapy (Gemcitabine, Cisplatin) should be administered on days 3 and 10. For Arm B, a separate Day 1 is not required; Day 1 and Day 3 procedures can be combined.

**Arm A:** Gemcitabine, cisplatin will be dosed on day 3 and 10 +/- 48 hours of each 3 week cycle. Veliparib will be dosed at 80 mg PO BID day 1- 12, q 3 weeks.

**Arm B:** Gemcitabine, cisplatin will be dosed on day 3 and 10 +/- 48 hours of each 3 week cycle.

Standard hydration (per institutional standard guidelines) will be used with this regimen. Approximately one liter normal saline will be given concurrently.

A CBC and creatinine will be checked prior to each treatment dosing. See study calendar ([section 10](#)).

For anti-emetic recommendations, see [section 5.3](#).

#### 5.1.3 Supportive Care Measures

The use of granulocyte colony stimulating factors (either G-CSF or pegylated filgrastim) is not routinely recommended but may be used as clinically indicated. The use of growth factors for the treatment of anemia is allowed at the discretion of the treating investigator.

Patients with known metastatic disease to the bones may be allowed to receive bisphosphonate therapy as directed by the treating investigator. Other concurrent supportive care is not restricted, including use of narcotics for pain control, anti-emetics, anti-diarrheals, pancreatic enzymes. No concurrent chemotherapy, immunotherapy or radiation therapy is permitted during protocol therapy.

## **5.2 Definition of Dose-Limiting Toxicity (DLT)**

Dose-limiting toxicity criteria applies to the non-randomized lead-in portion of Part I of the study (i.e., the first 6-24 patients enrolled in Part I).

DLT is defined as an adverse event that is related (possibly, probably or definitely) to administration of veliparib and gemcitabine and cisplatin and fulfils one of the criteria below. The DLT period applies to cycle 1 of the study.

- Grade  $\geq 3$  non-hematologic toxicity, felt to be related to study medications with the following clarifications:
  - Diarrhea Grade 3, will be dose-limiting only if refractory to treatment with loperamide as outlined in [section 5.3](#) below.
  - Nausea and Vomiting Grade 3 will only be considered dose-limiting if refractory to anti-emetic therapy and unable to be corrected to Grade 1 or less within 24 hours.
  - Rise in creatinine to Grade 3, not corrected to Grade 1 or less within 24 hours with IV fluids, will be dose-limiting.
  - Grade  $\geq 3$  metabolic toxicities unable to be corrected to Grade 2 or less within 24 hours, e.g., hyperglycemia, hypokalaemia, hypomagnesemia, hyponatremia, will be considered dose-limiting. Grade 4 metabolic toxicities (except hyperglycemia) will be considered dose-limiting regardless of duration.
- Grade 3 Thrombocytopenia with bleeding.
- Grade 4 Thrombocytopenia.
- Grade 4 Neutropenia.
  - Note any degree of anemia, leucopenia in the absence of grade 4 neutropenia, or lymphopenia, will not be considered dose-limiting.
- Febrile Neutropenia, defined as fever  $> 38.5$  and neutrophils  $< 0.5$ .
- Failure to initiate cycle #2 of therapy  $> 2$  weeks after planned start of next cycle.

## **5.3 General Concomitant Medication and Supportive Care Guidelines**

All patients will be provided with the best available supportive care measures.

In case participants develop nausea/vomiting/diarrhea or myelosuppression, supportive medications will be prescribed as per Clinical Center and ASCO

guidelines. Seizures were seen in some animal toxicology studies, although at doses much higher than those anticipated for this study. Seizures in animals were successfully treated with lorazepam.

Anti-Emetic Regimen for Gemcitabine, Cisplatin (+/- Veliparib), Arm A, B

The below are recommended suggestions for anti-emetic therapy.

- Pre IV chemotherapy: 5-HT3 antagonist, e.g. Palonosetron 0.25 mg IVPB  
Dexamethasone 4-12 mg PO, Aprepitant 125 mg PO.
- Day 2: Dexamethasone 4-8 mg PO in the morning, Aprepitant 80 mg PO in the morning.
- Day 3: Dexamethasone 4-8 mg PO in the morning, Aprepitant 80 mg PO in the morning.
- Alternatively fosaprepitant IV can replace aprepitant PO day 1-3.

As needed:

Metoclopramide 10 mg PO q 4-6 hrs PRN for nausea and vomiting.

Oral 5 HT3 antagonist, e.g., ondansetron 8 mg q 8 hrs PO PRN for nausea and vomiting.

Of note, many patients are likely to be either diabetic or have some degree of glucose intolerance, thus the dose of dexamethasone may be reduced or omitted as clinically appropriate by the treating investigator.

Each institution may use its own standard guidelines for the administration of anti-emetics. The above are a guideline.

Nausea/ Vomiting: Nausea and vomiting will be considered refractory if it does not resolve to  $\leq$  Grade 1 with at least 2 anti-emetics.

Diarrhea: If diarrhea develops and does not have an identifiable cause other than gemcitabine, cisplatin and veliparib, loperamide 4 mg po after the first unformed stool with 2 mg for every subsequent unformed stool. This regimen can be repeated for every diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 24 hours to  $\leq$  Grade 1 with the above regimen (max 16 mg loperamide/day).

Thrombocytopenia: Thrombocytopenia will be treated conservatively. In the absence of bleeding, fever, or a necessary invasive procedure, platelet transfusions should be given for a platelet count below 20,000/ $\mu$ L. Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Neutropenia: Febrile neutropenia is a life-threatening complication requiring hospitalization and prompt broad-spectrum antibiotics and evaluation for a source and microbial cause of the episode. As clinically indicated filgrastim may be initiated for

grade 4 neutropenia at the investigator's discretion. Study medications will not be re-instituted until at least 24 hours after filgrastim administration.

Anemia: Symptomatic anemia should be treated with red cell transfusion as clinically indicated and or/ if the hemoglobin falls below 8 mg/dl. Use erythropoietin-stimulating agents per standard of care National Comprehensive Cancer Network (NCCN) and/or institutional guidelines, iron supplements, and/or transfusions as clinically indicated for management of anemia. Prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) highlight that there is a potential risk of shortening the time to tumor progression or disease-free survival. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended. Aranesp, Epogen and Procrit may not alleviate fatigue or increase energy, and should not be used in patients with uncontrolled hypertension. The package inserts for these agents should be consulted.

Seizures: Seizures attributed to veliparib were identified in some animal toxicology studies, although at much higher doses than are to be utilized in this study. Seizures in animals were successfully treated with lorazepam. Therefore, lorazepam should be considered as a possible first choice for controlling seizures, should they occur on this study. One episode of seizure was seen in a patient treated in an ongoing phase I study of single-agent veliparib at a dose level of 400 mg PO BID. Any seizure occurring in the lead-in phase I portion will constitute a DLT.

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.

## **5.4 On-Study Radiologic Evaluations**

Patients will undergo baseline imaging within 4 weeks of start of protocol therapy.

For Part I (Arm A and B), radiologic re-staging will be performed every 6 weeks from the start of therapy (i.e., after every 2 cycles of therapy irrespective of treatment delays). The window period for performing on study imaging will be within +/- 5 days. After 6 months on study, scans can be done every 9 weeks +/- 5 days. After 18 months on study, scans can be done every 12 weeks +/- 5 days. Patients randomized to Arm A who continue on single-agent veliparib (per Arm C dosing) will have a scan every 8 weeks +/- 5 days for the first 2 scans, then every 12 weeks +/- 5 days. At the beginning of year 4, scans can be done every 16 weeks +/- 8 weeks.

For Part II (Arm C), radiologic re-staging will be performed every 8 weeks from the start of therapy (i.e., every 2 cycles of therapy irrespective of treatment delays). The window period for performing on study imaging will be within +/- 5 days. A CT scan with oral and IV contrast of the chest, abdomen, pelvis is the preferred choice of imaging. A non-contrast CT of the chest should be obtained for chest imaging for patients requiring an MRI of the abdomen/pelvis (with gadolinium).

Ideally the same imaging will be performed throughout the study, e.g., if baseline

MRI abdomen/pelvis with gadolinium, then for re-evaluation a MRI abdomen/pelvis with gadolinium should be obtained.

Following each radiologic assessment, images of all scans performed as part of the study should be sent to the PI at MSK. Images should be de-identified and in DICOM format before they are submitted to MSK. Images may be submitted via the MSK Secure File Transfer Program (preferred) or by mail.

Images sent by mail should be submitted in a CD/DVD DICOM format to the following address:

Eileen M. O'Reilly, M.D.  
Memorial Sloan Kettering Cancer Center  
300 East 66<sup>th</sup> street, 1021  
New York, NY 10065  
Tel: 646-888-4182  
Fax: 646-888-4542  
Email: [oreillye@mskcc.org](mailto:oreillye@mskcc.org)

## **5.5 Duration of Therapy**

In the absence of treatment delays due to adverse events, treatment may continue for as many cycles as required or until one of the following criteria applies:

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

## **5.6 Duration of Follow Up**

All patients will be followed for survival after removal from study at a minimum interval of every 3 months, or until death whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

## **5.7 Criteria for Removal from Study**

Patients will be removed from study when any of the criteria listed in [Section 5.5](#) applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

## 6. TREATMENT ADMINISTRATION/ DOSING DELAYS/ DOSE MODIFICATIONS

### General Information

Patients should meet the hematologic and creatinine laboratory parameters outlined in [section 3.1.6](#), with the exception of hemoglobin, before initiation of each cycle of therapy. Patients with a hemoglobin < 9.0 mg/dl may initiate a new cycle of therapy at the discretion of the treating physician. All toxicities (except alopecia, lymphopenia, hyperglycemia, hypoalbuminemia, hypomagnesaemia, electrolyte abnormalities) should have resolved to  $\leq$  Grade 1 severity before initiation of the next cycle of therapy.

Qualifying laboratory tests can be obtained up to 48 hours before planned initiation of therapy.

Dose adjustments will be made according to the organ system showing the greatest degree of toxicity. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting beginning April 1, 2018 (investigators may continue to collect and locally store AE data in CTCAE v4.0). A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

Initiation of the next cycle of therapy may be delayed ideally by no more than 3 weeks to allow recovery from toxicity related to treatment. Treatment delay of > 3 weeks due to toxicity that is related to protocol treatment may lead to removal from study except under certain medical circumstances and as discussed with the overall study PI.

No more than 3 dose reductions for each drug are allowed for each patient, before a patient will be taken off study. All dose reductions are typically permanent, with the possible exception of re-introduction of cisplatin therapy at a later time point if clinically indicated and no other limiting toxicity precludes this consideration. In addition, in discussion with the PI consideration of dose re-escalation of either cisplatin or gemcitabine may be considered on an individual patient basis.

#### **Arm A: Lead-In, Non-Randomized portion of Part I**

DLT criteria as per [section 5.2](#) apply to cycle 1. The starting dose of veliparib is 20 mg PO BID (dose level 0) day 1-12.

If none of the first 3 patients experience a DLT after completion of cycle 1 at dose level 0 of veliparib 20 mg PO BID day 1- 12, the veliparib dose will be increased to 40 mg PO BID day 1-12 (dose level 1) for the next cohort of patients and subsequently to 80 mg PO BID day 1-12 (dose level 2). If no DLT is observed in dose level 2, additional cohorts will be added as follows: dose level 2A: veliparib 80 mg po BID day 1-21 (continuous

dosing); dose level 3: veliparib 140 mg po BID day 1-21; dose level 4: veliparib 200 mg po BID day 1-21.

At any dose level, if either 2 of 3, or 2 of 6 experience a DLT, the maximum-tolerated dose (MTD) will be exceeded. The dose level chosen for the randomized portion of the study will be one dose level below the latter level. It is estimated that 6- 24 patients will be required for the non-randomized, lead in portion of Part I.

**Arms A and B: Gemcitabine, Cisplatin +/- Veliparib; Randomized portion Part I:**

Each cycle will be 3 weeks long. Veliparib will be dosed starting at 80 mg po BID on day 1-12 of each cycle (Arm A only). Gemcitabine and cisplatin will be dosed on day 3 and 10 of each cycle for Arm A and day 3 and 10 for Arm B. For Arm A, veliparib should start on Day 1 and chemotherapy should be administered on days 3 and 10. For Arm B, a separate Day 1 is not required; Day 1 and Day 3 procedures can be combined. For Arm B, day 1 and day 3 may overlap if necessary as there is a +/- 48 hour window for treatment.

If day 3 dosing of IV gemcitabine/cisplatin is held, the gemcitabine/cisplatin dosing will be delayed by one week. As far as possible, veliparib dosing will not be interrupted unless necessitated.

If day 10 dosing of IV gemcitabine/cisplatin is held, it will count as a missed week and will not be made up. As far as possible, veliparib dosing will not be interrupted unless necessitated.

Irrespective of treatment delays, all patients will undergo radiologic re-assessment every 6 weeks +/- 5 days. After 6 months on study, scans can be done every 9 weeks +/- 5 days. After 18 months on study, scans can be done every 12 weeks +/- 5 days. Patients randomized to Arm A who continue on single-agent veliparib (per Arm C dosing) will have a scan every 8 weeks +/- 5 days for the first 2 scans, then every 12 weeks +/- 5 days. At the beginning of year 4, scans can be done every 16 weeks +/- 8 weeks.

**Dose Levels for Gemcitabine, Cisplatin for Lead-in Non-Randomized and Randomized Phase II (Arm A, Arm B)**

Dose Level	Gemcitabine	Cisplatin
-3	300 mg/m <sup>2</sup>	10 mg/m <sup>2</sup>
-2	350 mg/m <sup>2</sup>	15 mg/m <sup>2</sup>
-1	500 mg/m <sup>2</sup>	20 mg/m <sup>2</sup>
<b>1 (start dose level)</b>	<b>600 mg/m<sup>2</sup></b>	<b>25 mg/m<sup>2</sup></b>

Laboratory requirements prior to each new cycle of therapy (day 1 or within 2 days of start of new cycle). For gemcitabine/cisplatin dosing determination for day 3, laboratory tests on day 1 of each cycle are acceptable.

- Absolute neutrophil count  $\geq 1,500/\text{mcL}$
- Platelets  $\geq 100,000/\text{mcL}$

- Creatinine  $\leq 1.5 \times \text{ULN}$
- A complete metabolic panel to be drawn, including, LDH, liver function tests (AST, ALT, bilirubin, alkaline phosphatase), electrolytes (Na, K, Ca, Magnesium, Phosphorus).
- Ca 19-9, CEA (at the start of every odd cycle of therapy, e.g., cycle 1, 3, 5, etc.).
- Patients with a hemoglobin  $< 8.0 \text{ mg/dl}$  may initiate a new cycle of therapy at the discretion of the treating physician.

Laboratory requirements prior to day 10 of therapy (within 0-2 days of dosing of IV gemcitabine/cisplatin therapy):

- Absolute neutrophil count  $\geq 1,000/\text{mcL}$
- Platelets  $\geq 75,000/\text{mcL}$
- Creatinine  $\leq 1.5 \times \text{ULN}$   
Optional biochemistry panel, phosphorus and magnesium as clinically indicated.

#### **Arm C: Veliparib single agent**

Each cycle will be 28 days in length. Veliparib will be dosed at 400 mg BID orally continuously (dose level 0). In addition to the dose levels below, in discussion with the PI, uneven dosing may be considered (e.g., 200mg am, 300mg pm), if that is deemed to be a better fit for a given patient to address issues of optimizing dose vs myelosuppression. This will apply to patients previously switched to Arm C (single agent veliparib).

#### **Dose Levels for Veliparib (ABT-888) Part II (Arm C)**

Dose Level	Veliparib (ABT-888)
-3	100 mg PO BID x 28 days (two 50-mg capsules BID or 1 x 100-mg capsule BID)
-2	200 mg PO BID x 28 days (four 50-mg capsules BID or 2 x 100-mg capsules BID)
-1	300 mg PO BID x 28 days (six 50-mg capsules BID or 3 x 100-mg capsules BID)
<b>0 (start dose)</b>	<b>400 mg PO BID x 28 days (eight 50-mg capsules BID or 4 x 100-mg capsules BID)</b>

Laboratory requirements prior to each new cycle of therapy (day 1 or within 2 days of start of new cycle):

- Absolute neutrophil count  $\geq 1,000/\text{mcL}$
- Platelets  $\geq 75,000/\text{mcL}$
- Creatinine  $\leq 1.5 \times \text{ULN}$

- A complete metabolic panel to be drawn, including, LDH, liver function tests (AST, ALT, bilirubin, alkaline phosphatase), electrolytes (Na, K, Ca, phosphorus).
- Ca 19-9, CEA (at the start of every odd cycle of therapy, e.g., cycle 1, 3, 5, etc.).
- Patients with a hemoglobin < 8.0 mg/dl may initiate a new cycle of therapy at the discretion of the treating physician.

## 6.1 Dose Modifications for Hematologic Toxicity

Dose modifications should be based on the suspected causative agent. Therapy will not be interrupted for Grade 2 hematologic toxicities.

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

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

### 6.1.1 Neutrophils

The following dose adjustments are based on the neutrophil nadir of the preceding treatment cycle.

#### **Arms A and B (Gemcitabine, Cisplatin +/- Veliparib)**

<b>Absolute ANC Nadir</b>	<b>Veliparib</b>	<b>Gemcitabine</b>	<b>Cisplatin</b>
Grade 3 (no fever)	No change	No change	No change
Grade 4 (no fever)	No change	Dose level -1	Dose level -1
Grade 3-4 (with fever)	No change	Dose level -1	Dose level -1
Grade 4 (no fever) 2 <sup>nd</sup> episode	No change	Dose level -2	Dose level -2
Grade 4 (no fever) 3 <sup>rd</sup> episode	No change	Dose level -2	Dose level -2
Grade 3-4 (with fever)	No change	Dose level -2	Dose level -2

#### **Arm C (Veliparib)**

<b>Absolute ANC Nadir</b>	<b>Veliparib</b>	<b>N/A</b>	<b>N/A</b>
Grade 3 (no fever)	No change		
Grade 4 (no fever)	No change		

Grade 3-4 with fever	Dose level -1		
Grade 4 (no fever) 2 <sup>nd</sup> episode	No change		
Grade 4 (no fever) 3 <sup>rd</sup> episode	Dose level-2		
Grade 3-4 (with fever)	Dose level-2		

Colony stimulating factors: Patients should not routinely receive prophylactic colony stimulating factors (e.g., G-CSF, GM-CSF) during cycle 1. Subsequent use will be at the discretion of the treating physician.

If a patient develops febrile neutropenia, ABT-888 should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours of the last dose of ABT-888 unless absolutely necessary. See [Section 5.3](#) for further details.

For Arm A and B, if patients experience recurrent grade 2 hematologic toxicity (platelets or neutrophils) that delays therapy on  $\geq 2$  occasions, the investigator may choose to decrease the dose of gemcitabine or cisplatin for subsequent cycles of therapy. In general gemcitabine should be decreased by 1 dose level first and subsequently cisplatin as needed. The investigator may choose to decrease both drugs together by 1 dose level also.

For Arm C, if patients have grade 1 or 2 hematologic toxicity (platelets or neutrophils), the investigator may choose to continue treatment or allow dose interruption for a maximum of 3 weeks. If patients have grade 3 or 4 neutropenia or thrombocytopenia, then patients should have dose interruption for a maximum of 3 weeks until recovered to CTCAE Grade  $\leq 1$ . Upon recovery, ABT-888 dose should be reduced by 1 dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce ABT-888 by 1 dose level.

#### 6.1.2 Platelets

##### **Arms A and B (Gemcitabine, Cisplatin +/- Veliparib)**

Nadir Platelet Count	Veliparib	Gemcitabine	Cisplatin
Grade 3-4 1 <sup>st</sup> episode	No change	Dose level -1	Dose level -1
Grade 3-4 2 <sup>nd</sup> episode	No change	Dose level -2	Dose level -2

##### **Arm C (Veliparib)**

Nadir Platelet Count	Veliparib	N/A	N/A
Grade 3-4 1 <sup>st</sup> episode	Dose level -1		
Grade 3-4 2 <sup>nd</sup> episode	Dose level -2		

#### 6.1.3 Myelodysplastic Syndrome (MDS)/ Acute Myeloid Leukemia (AML)

Patients should be monitored for persistent myelosuppression, including anemia, thrombocytopenia, and neutropenia that does not recover to normal or grade 1 between courses of treatment, as per Good Clinical Practice. If peripheral blood counts do not recover to normal or are persistently abnormal, the patient should be evaluated for the possible development of MDS/AML using a bone marrow aspirate with cytogenetics. Patients who develop MDS/AML on treatment should discontinue ABT-888 treatment and be managed appropriately. A complete history of prior therapy should be documented, particularly prior platinum-based or alkylating agent therapies. Documentation of germline BRCA mutation (*gBRCAm*) status, if known, should be recorded.

## **6.2 Dose Modifications for Non-Hematologic Toxicity**

Dose modifications should be based on the suspected causative agent. For grade 2 toxicity study medication(s) should be dose reduced at the discretion of the treating investigator and pertaining to the likely causative drug. For example, no dose reduction is recommended for alopecia, however, neurotoxicity may require a dose reduction of cisplatin or veliparib.

### Grade 3-4 Drug-Related Non-Hematologic Toxicities:

Doses of gemcitabine, cisplatin and veliparib will be held until toxicities recover to  $\leq$  Grade 1 (with the exception of electrolyte abnormalities, alopecia, hypomagnesemia, hypoalbuminemia), prior to initiating therapy at the next lowest dose level.

Electrolyte abnormalities will not require dose reduction if resolution to Grade 2 or less is documented after 48 hours.

Patients are allowed up to 3 dose level reductions on protocol.

### **6.2.1 Gastrointestinal Toxicity**

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

Please note for Arm C (single agent veliparib): Patients may manifest nausea. Dose reduction for non-tolerable grade 1-2 nausea is allowed. Dose reductions can be made during a treatment cycle or at the start of the next cycle. Dose reduction is preferable to prolonged treatment interruption or study discontinuation. Grade 3 (or higher) nausea requires reduction of one dose level and delay in subsequent therapy until nausea has recovered to  $\leq$  grade 1.

Anti-emetic guidelines for gemcitabine and cisplatin are in [section 5.3](#).

Diarrhea: Should be managed with appropriate anti-diarrheal therapy. Patients should be encouraged to take plenty of oral fluids. If symptoms do not decrease to grade 1 or less with adequate anti-diarrheal therapy, veliparib should be held until recovery from symptoms to < grade 1. Veliparib can be re-started at the same dose following recovery to < grade 1 if worst grade of toxicity is < grade 2). For worst grade > 3, re-start with dose reduction by one dose level.

It is recommended that loperamide be prescribed to control diarrhea, barring any contraindication to such therapy. Loperamide should be taken at 4 mg after the first episode of diarrhea, and can be repeated at a dose of 2 mg after each subsequent episode, not to exceed 16 mg/ day in total dose. If symptoms recur, the dose of veliparib should be re-started with a reduction by one dose level.

#### 6.2.2 Hypersensitivity Reactions

The below is a guideline for hypersensitivity reactions to cisplatin. However, such reactions may also be managed per institutional protocols. Patients who have had a mild to moderate hypersensitivity reaction have been successfully re-challenged, but careful attention to prophylaxis and monitoring of vital signs is recommended.

Mild symptoms: e.g., mild flushing, rash, pruritus - complete infusion. Supervise at bedside. No treatment required.

Moderate symptoms: e.g., moderate rash, flushing, mild dyspnea, chest discomfort - Stop infusion. Give intravenous diphenhydramine 25-50 mg, ranitidine 50 mg IVPB and intravenous hydrocortisone 100 mg.

Resume infusion after recovery of symptoms at a low rate, 20 mg/hr. For 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete. If symptoms recur, stop infusion. Record toxicity on treatment flow sheets.

Severe life threatening symptoms: e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria)-stop infusion. Give intravenous diphenhydramine, ranitidine and hydrocortisone. Add epinephrine or bronchodilators if indicated. If wheezing is present, that is not responsive to bronchodilators, epinephrine is recommended. The patient should not be re-challenged with cisplatin. Report as adverse event.

Rarely, hypersensitivity reactions to gemcitabine may occur. These should be

managed per institutional guidelines. Re-challenge and pre-medication with steroids, H1 and H2 blockers and a lengthened gemcitabine infusion (e.g., over 60 minutes +/- 10 mins) may be considered as clinically appropriate.

### 6.2.3 Other Toxicities

For any grade 3 or 4 toxicity not mentioned above, the treatment with the likely inciting agent should be withheld until the patient recovers to grade 1 or less toxicity. The treatment should then be resumed at one lower dose level. For grade 2 toxicities, withhold treatment until the patient recovers, then consider whether resumption of treatment at a one dose-level reduction is indicated. Dose reduction will be done for the drug that is most likely to have caused the toxicity. For grade 1 toxicities, no dose reduction should be made.

## 6.3 Discontinuation of Study Drugs

For Arm A (Gemcitabine, cisplatin, veliparib): If a patient experiences a limiting toxicity precluding continuation of gemcitabine (e.g., pneumonitis, hypersensitivity reaction), the investigator may choose to continue cisplatin and veliparib if the patient is experiencing benefit from therapy.

For Arm A: If a patient experiences a limiting toxicity from cisplatin (e.g., allergic/infusion reaction), the investigator may choose to continue gemcitabine with veliparib if the patient is experiencing benefit from therapy.

For Arm A: If a patient has had both gemcitabine and cisplatin discontinued and is otherwise benefitting from veliparib, the patient is allowed to remain on study and continue single-agent veliparib. In this particular setting, there is an option to continue single-agent veliparib per the single-agent dosing schedule for Arm C, e.g., veliparib 400 mg PO BID daily continuously. The dose of single-agent veliparib may be adjusted to levels outside of the specified dose levels if discussed with the MSK PI.

For Arm A: If a patient experiences a limiting toxicity precluding continuation of veliparib (e.g. MDS/AML, severe persistent anemia) the patient may be allowed to continue the other therapies if they are experiencing clinical benefit and the toxicity is not related to the other therapies, based on the opinion of the treating investigator, and after discussion with the Principal Investigator.

For Arm B (Gemcitabine, cisplatin): If a patient experiences a limiting toxicity precluding continuation of gemcitabine (e.g., pneumonitis), the investigator may choose to continue cisplatin alone if the patient is experiencing benefit from therapy.

For Arm B: If a patient experiences a limiting toxicity from cisplatin (e.g., allergic reaction), the investigator may choose to continue gemcitabine alone

if the patient is benefitting from therapy.

For both Arm A and B: There may be occasion where a study medication has been discontinued, e.g., cisplatin, where it is considered medically appropriate to re-introduce this drug at a later date. In this setting, a discussion should take place with the study Principal Investigator (MSK PI) and the reasons for re-commencement of the drug clearly documented in the medical record.

For Arm C: Patients should not be allowed to remain in the study if they are taking ABT-888 as monotherapy and have bone marrow findings consistent with MDS/AML or experience severe persistent anemia.

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

### 7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

#### 7.1.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) For ABT-888 (Veliparib, NSC 737664)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/aeguidelines.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification.

Frequency is provided based on 2310 patients. Below is the CAEPR for ABT-888 (Veliparib).

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

Version 2.4, May 13, 2018<sup>1</sup>

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>			
	Anemia		<b><i>Anemia (Gr 3)</i></b>
	Febrile neutropenia		<b><i>Febrile neutropenia (Gr 3)</i></b>
<b>GASTROINTESTINAL DISORDERS</b>			
	Abdominal pain		
	Constipation		<b><i>Constipation (Gr 2)</i></b>
	Diarrhea		<b><i>Diarrhea (Gr 3)</i></b>
Nausea			<b><i>Nausea (Gr 3)</i></b>
	Vomiting		<b><i>Vomiting (Gr 3)</i></b>
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>			
Fatigue			<b><i>Fatigue (Gr 3)</i></b>

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
INVESTIGATIONS			
	Lymphocyte count decreased		<i>Lymphocyte count decreased (Gr 4)</i>
	Neutrophil count decreased		<i>Neutrophil count decreased (Gr 4)</i>
Platelet count decreased			<i>Platelet count decreased (Gr 4)</i>
	Weight loss		<i>Weight loss (Gr 2)</i>
	White blood cell decreased		<i>White blood cell decreased (Gr 4)</i>
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		<i>Anorexia (Gr 2)</i>
	Dehydration		<i>Dehydration (Gr 3)</i>
	Hypophosphatemia		<i>Hypophosphatemia (Gr 3)</i>
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
		Treatment related secondary malignancy	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		<i>Dysgeusia (Gr 2)</i>
	Headache		<i>Headache (Gr 3)</i>
		Seizure	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
VASCULAR DISORDERS			
		Thromboembolic event <sup>2</sup>	

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

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

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

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

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

**EAR AND LABYRINTH DISORDERS** - Vertigo

**EYE DISORDERS** - Blurred vision

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

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

**HEPATOBIILIARY DISORDERS** - Hepatic failure; Hepatobiliary disorders - Other (cirrhosis)

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

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

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

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

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

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

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

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

**RENAL AND URINARY DISORDERS** - Dysuria; Hematuria; Proteinuria

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

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

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

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

## 7.1.2 Adverse Event List(s) for Commercial Agent(s)

### **Gemcitabine:**

Please refer to the FDA-approved package insert for gemcitabine for product information, extensive preparation instructions, and a comprehensive list of adverse events.

#### **Toxicities:**

**Flu-like syndrome:** Flu-like syndrome is manifested by fever, fatigue, myalgias, headache, and cough.

**Myelosuppression:** Myelosuppression is the usual dose-limiting toxicity. Infusions longer than 1 hour are associated with increased myelosuppression.

**Hepatotoxicity:** Mild elevations in hepatic transaminase levels occur in as many as two-thirds of patients, but are reversible.

**Dyspnea:** Dyspnea occurs in 10-23% of patients and is usually associated with a drug-induced pneumonitis. More often, dyspnea is likely associated with the underlying malignancy.

**Gastrointestinal:** Nausea, vomiting, and anorexia are common but usually of mild to moderate severity. Stomatitis and diarrhea or constipation occur less often.

Nephrotoxicity: Proteinuria and hematuria are usually asymptomatic though they occur frequently. A serious hemolytic-uremic syndrome occurs in less than 1% of patients.  
Nervous system: Paresthesia and peripheral neuropathies occur in 2-10% of patients.  
Hypersensitivity reactions: Allergic reactions including bronchospasm have been reported in 4% of patients.  
Dermatologic: Minimal alopecia (15%) and macular or maculopapular rashes have been reported.

### **Cisplatin**

Please refer to the FDA-approved package insert for cisplatin for product information, extensive preparation instructions, and a comprehensive list of adverse events.

#### **Toxicities**

Hematologic: Neutropenia, anemia, thrombocytopenia.

Gastrointestinal: Nausea, vomiting.

Hepatic: Transient elevation in AST, ALT, alkaline phosphatase, bilirubin.

Neurologic: Ototoxicity (tinnitus, hearing loss), peripheral neuropathy.

Metabolic: Electrolyte disturbances, principally hypomagnesemia, hypocalcemia, hypokalaemia.

Miscellaneous: Anaphylactoid reactions, hypersensitivity, alopecia.

## **7.2 Adverse Event Characteristics**

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018 (investigators may continue to collect and locally store AE data in CTCAE v4.0). All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).
- **‘Expectedness’:** AEs can be ‘Unexpected’ or ‘Expected’ (see [Section 7.1](#) above) for expedited reporting purposes only. ‘Expected’ AEs (the ASAEs) are ***bold and italicized*** in the CAEPR ([Section 7.1.1](#)).
- **Attribution of the AE:**
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

## **7.3 Expedited Adverse Event Reporting**

For protocols with CAEPRs not including a “SPEER” category, protocol-specific exceptions to the CTEP-AERS reporting table can be found in the CAEPR’s

“ASAEL” category instead. This protocol-specific exception is limited to Grade 1 and Grade 2 ASAEL events, *i.e.* Grade 3 through Grade 5 ASAEL-listed events are NOT exceptions to CTEP-AERS reporting.

- 7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (<http://ctep.cancer.gov>). The reporting procedures to be followed are presented in the “CTEP, NCI Guidelines: Adverse Event Reporting Requirements” which can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). These requirements are briefly outlined in the table below ([Section 7.3.3](#)). In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

### 7.3.2 Reporting for Participating Centers

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

In addition to reporting to CTEP-AERS:

- Participating sites are responsible for submitting all SAEs to their local IRB per institutional guidelines
- Participating sites are responsible for reporting all SAEs to the MSK PI via e-mail within 3 calendar days of learning of the event. Participating sites should notify the MSK PI of any grade 5 event immediately.
- Participating sites should use the SAE Report Template to report SAEs to MSK.

For non-N01 contract holders, relevant source documentation should also be submitted to MSK along with the SAE CRF, to be reviewed against the data as it is entered.

**SAE contact information for the Coordinating Center is listed below:**

**Study Coordinator (for participating sites):**

Shreya Vemuri  
Memorial Sloan Kettering Cancer Center  
633 3<sup>rd</sup> Avenue, 15<sup>th</sup> Floor  
New York, NY 10017  
Tel: (646)-603-4018  
Email: [vemuris@mskcc.org](mailto:vemuris@mskcc.org)

**Eileen M. O'Reilly, M.D. (MSK PI)**  
Memorial Sloan Kettering Cancer Center  
300 East 66<sup>th</sup> Street, Office 1021

New York, NY 10065  
Tel: (646) 888-4182  
Fax: (646) 888-4542  
Email: [oreillye@mskcc.org](mailto:oreillye@mskcc.org)

The MSK Research Staff is responsible for submitting all SAEs to the MSK IRB/PB within 5 days of learning of the event.

### Safety Reports:

MSK must submit outside safety reports to the MSK IRB/PB according to institutional guidelines. All outside safety reports will be made available to the participating sites. Outside safety reports that are reportable to the MSK IRB/PB will be distributed to the participating sites immediately upon receiving a stamped copy from the MSK IRB/PB. Participating sites will receive a special alert for any outside safety reports that warrant a significant change to the conduct of the study. Outside safety reports that are not reportable to the MSK IRB/PB, will be sent to the participating sites monthly.

Participating sites are responsible for submitting safety reports to their site IRB per their local guidelines. All site IRB approvals/acknowledgments of safety reports must be sent to MSK upon receipt.

### 7.3.3 Expedited Reporting Guidelines

### Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention <sup>1, 2</sup>

#### FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for  $\geq 24$  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 serious 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table [below](#).

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization $\geq 24$ hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization $\geq 24$ hrs	Not required	

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

**Expedited AE reporting timelines are defined as:**

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

<sup>1</sup>Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

<sup>2</sup> For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011

## **7.4 Routine Adverse Event Reporting**

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

## **7.5 Secondary AML/MDS**

AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v5.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

## **7.6 Serious Adverse Event (SAE) Reporting for MSK**

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious 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

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

The SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to [saegrade5@mskcc.org](mailto:saegrade5@mskcc.org). All other reports should be sent to [sae@mskcc.org](mailto:sae@mskcc.org).

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following:
  - An explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

#### Responsibilities of Participating Sites

- Participating sites are responsible for reporting all SAEs to their site IRB per local guidelines. Site IRB approvals/acknowledgments must be sent to MSK upon receipt.
- Participating sites are responsible for submitting the SAE Report form to MSK within 3 calendar days of learning of the event.

- When a life-threatening event or death is unforeseen and indicates participants or others are at increased risk of harm, participating sites should notify the MSK PI as soon as possible but within 24 hours of the time the site becomes aware of the event.
- For studies that require CTEP-AERS reporting, participating sites can submit directly through CTEP-AERS and copy the MSK PI and designees.

#### Responsibilities of MSK

- MSK is responsible for submitting all SAEs to the MSK IRB/PB and funding entities (if applicable) as described in the protocol.
- MSK is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 15 days of receiving the stamped SAE report from the MSK IRB/PB.
- MSK is responsible for informing all participating sites within 24 hours or on the next business day about a life-threatening event or death that is unforeseen and indicates participants or others are at increased risk of harm.

### **7.7 Unanticipated Problems**

Unanticipated problems involving risks to participants or others (UPs) are defined as any incident, experience or outcome that meets all of the following criteria:

- Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; **and**
- Related or possibly related to participating in the research (possibly related means there is a reasonable probability that the incident, experience or outcome may have been caused by procedures involved in the research); **and**
- Suggests that the research place participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Participating sites are responsible for reporting all UPs to MSK as soon as possible but within 3 calendar days of learning of the event. UPs that are SAEs should be reported to MSK via SAE Report form as per section [7.6](#) of this protocol. All other UPs should be reported to MSK in a memo signed by the site PI.

MSK is responsible for submitting UPs to the MSK IRB/PB according to institutional guidelines. In addition, MSK is responsible for notifying participating sites of all non-SAE UPs that may affect the sites.

## **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](#).

## 8.1 CTEP IND Agent Veliparib (ABT-888, NSC 737664)

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

**Other Names:** A-861695.0

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

**Molecular Formula:** C<sub>13</sub>H<sub>16</sub>N<sub>4</sub>O      **M.W.:** 244.29

**Description:** White opaque capsule

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

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

**Storage:** Store intact bottles between 15° 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.

### Availability

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

Veliparib is provided to the NCI under a Collaborative Agreement between Abbott Laboratories and the DCTD, NCI (see [Section 12.9](#)).

#### 8.1.1 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by the responsible investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating

institution must be registered with CTEP, DCTD, through an annual submission of FDA Form 1572 (Statement of Investigator), Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Agent may be requested electronically to PMB. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application <https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jsp>. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account <https://ctepcore.nci.nih.gov/iam> and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov) anytime.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator’s Handbook for Procedures for Drug Accountability and Storage.)

Investigator Brochure Availability – The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status and a “current” password. Questions about IB access may be directed to the PMB IB coordinator at [IBCoordinator@mail.nih.gov](mailto:IBCoordinator@mail.nih.gov).

As of April 27, 2023, AbbVie will discontinue the ABT-888 (veliparib). No additional drug supply will be available for ordering after December 31, 2024.

## 8.2 Gemcitabine

**Chemical Name:** 4-amino-1-(2-deoxy-2,2-difluoro- $\beta$ -D-erythro-pentofuanosyl)pyrimidin-2(1*H*)-on 2',2'-difluoro-2'-deoxycytidine.

**Other Names:** Gemzar<sup>®</sup>, Eli Lilly and Company.

**Classification:** Antimetabolite: Nucleoside analog.

**Molecular Formula:** C<sub>9</sub>H<sub>11</sub>F<sub>2</sub>N<sub>3</sub>O<sub>4</sub>

**M.W.:** 263.198 g/mol

**Description:** Lyophilized powder.

**Product description:** Gemcitabine Hcl (2'2'-difluorodeoxycytidine) is a nucleoside analogue in the pyrimidine antimetabolite class. It is commercially available as a powder for reconstitution in 200 mg, 1 g and 2 g vials (lyophilized powder).

**Solution preparation:** Reconstitute the 200 mg vial with 5 mL preservative-free 0.9% NaCl; the 1 gram vial with 25 ml preservative-free 0.9% NaCl, or the 2 gram vial with 50 ml preservative-free 0.9% NaCl. The resulting solution is approximately 38 mg/mL. Then the desired amount should be measured/ withdrawn for vial(s) and diluted in 0.9% NaCl for infusion to a final concentration = 0.1-10 mg/ml.

**Storage and stability:** The intact vials should be stored at controlled room temperature 59°-86°F (15°-30°C). Reconstituted vials are stable for 7 days at room temperature. Refrigerated infusions prepared in normal saline are stable for 7 days. Prepared infusions in normal saline are stable for 7 days at room temperature.

**Route of administration:** Short intravenous infusion over 30 minutes.

**Other:** Please refer to the FDA-approved package insert for gemcitabine should additional information on gemcitabine be required.

### **Cisplatin**

**Chemical Name:** (SP-4-2)-diamminedichloridoplatinum.

**Other Names:** Cisplatinum, cis-diamminedichloroplatinum(II), CDDP, Platinol, Platinol-AQ.

**Classification:** Alkylating-like agent.

**Molecular Formula:** H<sub>6</sub>Cl<sub>2</sub>N<sub>2</sub>Pt                      **M.W.:** 301.1 g/mol

**Description:** Aqueous solution.

**Product description:** Heavy metal bi functional alkylating-like agent. Cisplatin has complete bioavailability, >95% protein binding, has a half-life of 30- 100 hours and is renally excreted.

**Solution preparation:** Cisplatin is commercially supplied as a lyophilized powder in 10 mg and 50 mg vials, and stored at room temperature. The drug should be reconstituted using 10 ml and 50 ml respectively of sterile water for injection, USP to yield a concentration of 1 mg/ml. Cisplatin doses of < 50 mg/m<sup>2</sup> should be diluted in a 50ml normal saline infusion bag and can be administered over 30 minutes. Needles and IV sets using aluminum should not be used in the administration of cisplatin.

**Storage and stability:** Store vials at room temperatures. Infusions prepared in normal saline are stable for 48 hours. Do not refrigerate. Once a multidose vial has been entered, the remaining cisplatin is stable for 28 days when protected from light.

Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature (25° C, 77° F).

The reconstituted solution is stable for 20 hours at room temperature (25° C, 77° F). Solution removed from the amber vial should be protected from light if it is not to be used within six hours. Important Note: Once reconstituted, the solution should be kept at room temperature (25° C, 77° F). If the reconstituted solution is refrigerated a precipitate will form.

**Route of administration/ Hydration:** Short intravenous IVPB infusion with secondary set over 30 minutes. Cisplatin is an irritant. For doses < 50 mg/m<sup>2</sup> administer normal saline at 350 mL/hr for 1 liter total.

**Other:** Please refer to the FDA-approved package insert for cisplatin should additional information on cisplatin be required.

## 9. CORRELATIVE/SPECIAL STUDIES

### 9.1 Laboratory Correlative Studies

MSK will lead the correlative studies which will be coordinated by Dr. Eileen O'Reilly and which will be performed in conjunction with several of the MSK Core Laboratory facilities and with the Center for Pancreas Cancer Research and other collaborators detailed below.

For the non-randomized, lead-in portion of Part I, archival tumor specimens will be obtained. No new research biopsies or blood/serum will be obtained for patients treated as part of this 6-24 patient cohort.

For the randomized portion of Part I, archival tumor specimens, new biopsies and serum/blood will be obtained as outlined below.

**Aim 1:** To determine the genotype of BRCA1, BRCA2 and PALB2- associated pancreas cancer.

**Resource:** Pre-treatment biopsy (from patients in Part I, Arm A and Arm B; N= 24). Biopsies will be performed at selected sites.

**Hypothesis:** Due to the genetic instability incurred by defective homologous repair, we hypothesize that pancreas adenocarcinoma arising in carriers of BRCA1, BRCA2 or PALB2 germ line mutations will differ from sporadic pancreas adenocarcinoma arising in patients not carrying such mutations in acquired somatic mutations within the pancreatic cancer. These differences may result in differential clinical patient outcomes and response to therapy. The candidate gene list to be evaluated is in [Appendix D](#) (updated regularly) and as of 2022 includes > 500 genes.

**Aim 2:** Assess tumor biopsies taken during treatment and at the time of tumor progression therapy for novel or persistent genetic alterations in genes examined in aim 1. (First priority for end of study biopsy).

**Resource:** Biopsies obtained during protocol therapy and post therapy biopsies obtained at the time of discontinuation of protocol therapy due to progression of disease. These biopsies will be obtained from Arm A and Arm B; N= 24-48.

**Hypothesis:** Resistance to therapy with veliparib and platinum chemotherapy agents in BRCA or PALB2-associated pancreas adenocarcinoma may arise due to altered expression in DNA damage, repair and cell survival pathways, or due to a genetic reversion of BRCA gene mutation to wild-type sequence which restores repair function <sup>69</sup>.

**Tumor Biopsies Before During and Following Treatment:** Identify differences in DNA sequence that correlate with acquired or inherent resistance and sensitivity to therapy with cisplatin, gemcitabine +/- veliparib in BRCA1, BRCA2 or PALB2-mutated pancreatic cancer. These differences may assist in determining the molecular mechanisms involved in therapeutic resistance.

**Aim 3:** There are two parts to this aim.

- a) To quantify levels of PAR in peripheral blood mononuclear cells (PBMCs), and tumor tissue (where available) at sequential time points before, during and following veliparib treatment.
- b) To quantify levels of  $\gamma$ H2AX and RAD51 foci in PBMCs, and tumor tissue (where available) at sequential time points to assess for formation of double-stranded DNA breaks, stalled/collapsed replication forks and evaluate homologous recombination competence.

**Resource:** PBMCs, and Tumor Biopsies. Pharmacodynamic studies to evaluate the effect of veliparib on tumor and non-tumor tissue.

**Hypothesis:** Levels of PARP inhibition and markers of DNA damage and repair in non-tumor tissue will be indicative of effective dosing in patients treated with veliparib.

**Aim 4 (Exploratory Aim):**

- a) To correlate the results of genotyping with gene expression to provide functional information on mutations identified.
- b) To conduct an exploratory assessment of differential expression of genes involved in DNA repair pathways pre, during and post treatment to identify candidate genes predictive of response or resistance to therapy for further study in preclinical models of disease.
- c) Immune correlative analyses (see below)

#### 9.1.1 Analyses for Correlative studies

Correlative studies will be performed on patients participating in Part I of the trial (Arms A and B), along with collection of archived tissue (see [below](#)) which will be collected for all patients including patients participating in Part II (Arm C) and the lead-in portion of Part I.

### **Geoffrey Beene Translational Core Facility:**

The Geoffrey Beene Translational Oncology Core Facility will be responsible for processing of clinical samples including DNA and RNA extraction, genotyping and gene expression analysis. It is located on the 6th floor of the Mortimer Zuckerman Research Building at MSK, in five processing rooms fully equipped to perform state of the art genome-scale molecular profiling technologies. The Core Manager, Dr. Adriana Heguy, is an expert in genetics and genomics and has vast experience in the management and analysis of large data sets generated by automated high throughput technologies, acquired in biotech and in academic settings. The Core is staffed with four technicians and one bioinformatician. The main automation equipment consists of one Biomek FX with capacity for setting up 27,648 PCR reactions daily, two Biomek NX, and one Biomek 3000, all custom-configured for high throughput DNA extractions, high throughput set up of PCR reactions and for cherry-picking, an automated plate sealer and a Duncan water bath thermal cycler with three computer controlled water baths to modulate the temperatures of the PCR reaction and a robotic arm to move the plates between water baths, with capacity for running 24 plates (9,216 PCR reactions) in ~ 2 hours. The Core laboratory also has a full Sequenom MassARRAY® compact system with Server and RT workstation, including: MassARRAY Analyzer Compact MALDI-TOF mass spectrometer for separation, detection and characterization of the analytes, the Nanodispenser RS 1000, and a Matrix PlateMate 2X3 for the post-PCR liquid handling steps. It has licenses to run genotyping as well as DNA methylation analysis using the MassARRAY system. The Core also has a NanoString nCounter system, including the nCounter Prep Station and the nCounter Analyzer, for gene expression, copy number variation and miRNA, using color-coded molecular barcodes that can hybridize directly to nucleic acids.

### **Genotyping:**

Fresh frozen tumor tissue obtained by core biopsy prior to commencement of study and following completion of study treatment will be used for genotyping studies. Sections will be reviewed by the reference pathologist to ensure that samples contain adequate cellularity and microdissection will be performed as needed. Germline DNA obtained from blood samples on all patients pre therapy will also be sequenced.

Genomic DNA will be isolated from frozen tissue by AllPrep DNA/RNA Mini Kit (Qiagen). 250 ng of DNA per sample will be required.

Tumor samples and matched germline DNA will be sequenced for mutations in over 400 target genes (see [Appendix D](#)). These genes include oncogenes and tumor suppressor genes commonly mutated in pancreatic cancer as well as a wider selection of candidate genes. This targeted gene sequencing platform (IMPACT) has been developed at MSK by Dr Berger, who will lead this aspect of the study. Custom oligonucleotides will be used to capture all exons of the target genes, with exon capture performed by hybridization (Agilent SureSelect Target Enrichment System) followed by next generation sequencing (Illumina HiSeq). This gene set is constantly being updated and thus by the time the analyses are being conducted is likely to be significantly in excess of the 411 genes listed. The accuracy and reproducibility of this platform has been demonstrated internally at MSK, and while the list maybe considered to be conservative the results are likely to be very reliable.

### Advantages of Selected Technique

This method of genotyping will allow the identification of sequence variants, small insertions and deletions and copy number alterations in the target genes. By sequencing tumors and matched normal's together we can also differentiate between somatic mutations and germline polymorphisms and identify regions of loss of heterozygosity. By sequencing pre, during and post treatment samples we will be able to assess for the presence of reversion mutations in *BRCA1*, *BRCA2* as well as other treatment induced genetic alterations<sup>70</sup>.

### Assessment of PAR Levels and $\gamma$ H2AX Foci Quantification:

PAR levels in PBMCs and tumor cell lists will be assessed using a validated immunoassay with purified monoclonal antibody to PAR as the capture reagent and rabbit anti-PAR antiserum (Trevigen Inc, Gaithersburg, MD) as the detecting agent with antirabbit horseradish peroxidase conjugate as the chemiluminescence reporter<sup>71</sup>.

#### **PAR Immunoassay**

##### Outcome Measure

PAR levels from specimens will be reported as pg/mL and as pg of PAR per 10<sup>7</sup> PBMCs isolated. PAR levels will be compared from baseline and from predetermined time points to derive a percentage change. PAR immunoassay will be performed at the University of Pittsburgh Cancer Institute.

##### Assessment

PAR concentration is determined on fresh samples by immunoassay (Kinders *et al.*, 2008). Briefly, 96-well microtiter plates were coated with a monoclonal antibody specific for PAR. After a blocking step, samples are diluted into a buffer and incubated with samples (16 hours at 4°C). Following a washing step, rabbit antiserum to PAR is added to each well, and an additional 2-hour incubation (at 22°C) is performed. Another washing step is performed, and a peroxidase-conjugated anti-rabbit antibody is added to each well, and incubated for 1 hour (at 22°C). Wells are washed again, a luminol substrate is added, and the assay wells are read in a Tecan luminometer. A set of calibrators and assay controls set at different PAR levels are run with each assay.

### $\gamma$ H2AX Foci Quantification:

Quantification of  $\gamma$ H2AX in PBMCs will be performed using a validated immunohistochemistry-based staining assay. The assay uses a biotinylated- $\gamma$ H2AX monoclonal antibody as the detector and an Alexa Fluor 488-streptavidin conjugate (Strp488) as the reporter for immunostaining.

Both of these methods will be carried out as per the standard operating procedures (SOP) detailed in the NCI Division of Cancer Treatment and Diagnosis (DCTD) website available at: <http://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm>

### Gene Expression Analysis:

Fresh frozen tumor tissue obtained by core biopsy prior to commencement of study treatment, during study treatment, and at time of disease progression will be used for gene expression analysis. Sections will be reviewed by the reference pathologist to ensure that samples contain adequate cellularity. This is the lowest priority study to be performed on the

available tissue and will only proceed when sufficient tissue resources have been allocated to Aims 1-3.

RNA will be isolated from frozen tissue by AllPrep DNA/RNA Mini Kit (Qiagen) and quantified by Nanodrop spectrophotometry<sup>72</sup>.

Transcriptome analyses by RNAseq will be performed in the Genomics Core laboratory under the direction of Dr Agnes Viale. Approximately 500ng total RNA per sample will be used.

#### Advantages of Selected Technique:

RNA-Seq is a sequencing based method that allows the entire transcriptome to be surveyed in a very high-throughput and quantitative manner. This method offers both single-base resolution and ‘digital’ gene expression levels at the genome scale.

### **Effect of PARPi on Peripheral and Tumor Immune Profile and Gene Expression:**

#### **Introduction**

Pancreatic cancers arising in the setting of a BRCA mutation are associated with increased sensitivity to platinum agents because of ineffective DNA repair, and the strategy of combining platinum therapy (cisplatin) and PARP inhibitors is an effective regimen in advanced gBRCA/PALB2+ pancreatic ductal adenocarcinoma. However, the underlying immune changes in the tumor and periphery which influence the responses are poorly understood.

#### **Objective**

To identify changes in immune cell infiltrate and cytokine profile within the primary tumor and peripheral blood to determine changes in immune signature that predict responsiveness to treatment.

#### **Study Population and Clinical Data**

We will include patient samples from previously conducted clinical trial including patients with untreated locally advanced or metastatic gBRCA/PALB2+ pancreatic ductal adenocarcinoma. N= 50 patients completed the study protocol (NCT01585805), between January 2014 and November 2018 at six sites in three countries

Arm A → Gemcitabine/Cisplatin/Veliparib (n=27)

Arm B → Gemcitabine/Cisplatin (n=23)

Clinical variables including time of diagnosis, CA19-9 levels, RECIST criteria for tumor response, time to progression and overall survival are collected in a prospectively maintained database.

#### **Changes in Peripheral Immune Cells:**

In this study we will identify changes in peripheral immune cell types including changes in number and function at three specific time points over the course of treatment. Previously collected and cryopreserved PBMCs will be used to perform flow cytometry analysis and to determine the following cell types.

- Neutrophils
- Monocytes
- Macrophage subtypes (M1 and M2)

- Dendritic cells
- CD4/CD8 cell subtypes
- NK and B cells

### **Flow Cytometry**

Utilizing previously established protocols, single cell suspensions from tumors and PBMCs will be assessed for viability with Trypan Blue and counted, then incubated with Fc receptor blocking solution followed by fluorophore-conjugated antibodies (BioLegend). For intracellular staining, cells will be permeabilized and stained with appropriate antibody per manufacturer's instructions (eBioscience). Flow cytometry will be performed on a Cytex™ Aurora, housed jointly in, and dedicated for the use of, the Brown and Vardhana labs, and analyzed using FloJo Version X (Tree Star).

### **Myeloid Cell Markers:**

Gating on CD45+ cells, CD11b, CD3, CD4, CD8, CD19, CD56, CD14, CD16, CD39, CD45RA, CCR7, CD27, CD39, TIGIT, PD1, CD25, CD38, CXCR3, CCR6, CCR4, GATA3, Tbet, FOXP3, Ki67, IgD, BTLA, CXCR4, and Granzyme B (GzmB) in various panels.

**T-Cell Markers:** (i) CD45+CD3+CD56–CD8+ and (ii) CD45+CD3+CD56–CD4+.

#### CD4+ Cell Markers:

CD45RA, CCR7, CD27, CD28, HLA-DR, CD71, CD25, CXCR5, CD39, TIGIT, PD1, CXCR3, CCR4, GATA3, Tbet, FOXP3, ICOS, RORyt, TCF1/7, Eomes, Ki67, GzmB, CCR6, and Perforin.

#### CD8+ T Cell Markers:

CD45RA, CCR7, CD27, CD28, HLA-DR, CD71, CD39, TIGIT, LAG3, TIM3, PD1, CD25, CXCR3, CCR4, GATA3, Tbet, TCF1/7, Eomes, Ki67, GzmB, CXCR4, IFN $\gamma$ , IL-2, Perforin.

### **Tumor Immune Gene Expression**

To understand how different treatments could change the tumor microenvironment, we will evaluate immune gene expression and cytokine production at various time points over the course of treatment.

Tumor samples (pre-treatment and post treatment) will be prepared to perform RNA sequencing using standardized protocols. Several pathways for immune gene expression will be analyzed for changes in various gene expression including: Immune infiltrate: CD4, CD8, FoxP3, CD68, CD163, Immune check point: CTLA-4, PD1, PDL1, PDL2, Alternative immune checkpoint: VISTA, TIM-3, LAG-3, Immune check point activation: CD27, CD137, GITR, CD40, OX40, ICOS, Myeloid immune suppression: CCL2, CCR2, CSF1R, IDO1, IL10, TGF $\beta$ .

Cytokine expression in the peripheral blood (PBMCs) and serum/plasma will also be assessed using RNA sequencing and ELISA using standardized protocols.

### **Immunohistochemistry**

Multiplex Immunohistochemistry will be utilized to assess various immune infiltrates and changes in patterns of immune cell infiltration within the primary tumor with various treatments.

### **TCR Sequencing**

Although the addition of veliparib to the combination of gemcitabine and cisplatin did not alter clinical outcomes, we hypothesize that the addition of PARPi to the therapy may increase neoantigen production and lead to more antigen presentation and T cell activation. If we identify changes in global T cell activation through deep immunophenotyping as described above, we will next move to submit PBMCs (+/- intratumoral T cells) for TCR sequencing, through a collaboration with Ben Greenbaum here at MSKCC, to profile the TCR repertoire diversity and clonality.

### Statistical Analyses

GraphPad Prism7 will be used for all statistical analyses. Differences between groups or experimental conditions will be determined using a two-tailed Mann–Whitney Wilcoxon test. Correlations were analyzed using Pearson correlation. Survival probabilities will be estimated using the Kaplan–Meier method and survival differences will be compared using the log-rank test. Two-sided *P* values <0.05 will be considered as statistically significant for all the analysis.

#### 9.1.2 Collection of Correlative Study Samples (Tissue and Blood)

Correlative studies will be performed on patients participating in **Part I** of the trial (Arms A and B), with the exception that archived tissue will be collected for all patients participating in the study, including the lead-in portion of Part I, **Part I** (Arm A and B) and **Part II** (Arm C).

#### Timing of specimen collection:

Specimen	Patients	Time of collection
Archival Tumor Tissue	All patients enrolled to part I and part II including patients enrolled in the lead-in, non-randomized portion of part I.	Preferably before any protocol therapy is administered but may be collected at any time during the first 3 cycles of therapy.
Research Blood	All patients enrolled to arms A & B of Part 1 (except patients enrolled in the lead-in, non-randomized portion of Part I).	<p><b>1<sup>st</sup> sample:</b> Within 10 days before the first dose of any protocol therapy (including the day of the first dose).</p> <p><b>2<sup>nd</sup> sample:</b> To be drawn while the patient is receiving veliparib (if on Arm A) between days 3-12 of cycle #2 or cycle #3.</p> <p><b>3<sup>rd</sup> sample:</b> At the time of off treatment assessments, or within 28 days of the last dose of study therapy.</p>
Tumor Biopsy (new procurement)	First 20 patients enrolled to arms A & B of Part 1 with disease accessible to biopsy and if it does not pose as a safety risk (except patients enrolled in the lead-in, non-randomized portion of Part	<b>1<sup>st</sup> biopsy:</b> Before initiation of therapy, obtain after patient has signed consent for the study and within 14 days prior to start of protocol therapy.

	I).	<p><b>2<sup>nd</sup> biopsy:</b> <u>ARM A:</u> To be obtained between days 3-12 of cycle #2 or cycle #3. <u>ARM B:</u> To be obtained anytime during cycle #2 or cycle #3.**</p> <p><b>3<sup>rd</sup> biopsy:</b> At the time of disease progression <math>\pm</math>, obtain up to 28 days after the last dose of protocol therapy.</p>
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\*Preferably liver, peritoneum or lung and not the primary tumor site, when metastatic disease is present. Patients will not undergo a research biopsy if it poses a safety risk or would delay treatment unnecessarily. For patients with localized pancreas adenocarcinoma, research microcore biopsies of the primary can be obtained if deemed feasible and safe.

\*\*If a patient refuses during-treatment biopsy, this will not be a violation. The timing of the 2<sup>nd</sup> during-treatment biopsy is flexible, however biopsies collected outside of this window must be discussed with the MSK PI.

$\pm$  anticipated to be feasible in approx 75% of the 40 patients.

^ Specimens should be collected prior to drug administration. day of collection. Five tubes of blood are to be collected as described in [Appendix C](#). Each tube should contain 8-10 ml of blood. Peripheral blood mononuclear cells, serum and buffy coat will then be isolated per standard processing procedures and stored with intent to perform the studies described herein and to perform future retrospective analyses.

#### 9.1.2.1 Procedures for Blood Specimen Retrieval and Processing:

##### **Blood Samples:**

The following specimens to be obtained at each of 3 specified time points:

- 2 x 8-10 ml BD vacutainer CPT tube with sodium citrate (black/blue top), to be processed within 2 hours of blood draw AND
- 2 x 8-10 ml BD vacutainer CPT tube with sodium citrate (black/blue top), to be processed within 2 hours of blood draw AND
- 1 x 10 ml BD vacutainer tube with clot activator (red top tube) to be processed within 1 hour of blood draw.

Processing of samples (at study site): Extraction of PBMCs, Serum and Buffy Coat  
See [Appendix C](#)

#### 9.1.3 Tumor Tissue

##### **Archival Tumor Tissue (Part I, II)**

Archival tissue will be obtained on all patients where available; paraffin block or 8-10 unstained slides. We anticipate 16-25 patients per each arm (A, B, C) for total of 48 to 60 tissue samples. We recognize many of these samples will be limited (e.g., FNA diagnostic samples) and not adequate for additional testing hence the need for prospective biopsies.

- Archival tissue specimens will ideally be collected before any protocol therapy is

administered. However, archival specimens can be collected at any time during the first 3 cycles of therapy.

### **Tumor Biopsies - New procurement (Part I)**

Tumor biopsies will be obtained on up to 20 patients/per arm with disease accessible to biopsy (preferably liver, peritoneum or lung and not the primary tumor site) enrolled on both arm A and B of the randomized phase II trial (40 total) at 3 time points, prior to dosing of any study drugs, during study treatment at the time of tumor re-staging (approximately week #6) and at the time of progression. Patients will not undergo a biopsy if it poses a safety risk or would delay treatment unnecessarily. If a patient refuses a biopsy it will not preclude them from participating in the study. While theoretically this would total 120 biopsies, we recognize that it will not always be possible to obtain a 2<sup>nd</sup> or 3<sup>rd</sup> biopsy for an individual patient at the time of progression of disease, and hence, we anticipate a total of approximately 60-100 biopsies. Tumor biopsies will be obtained from patients participating at selected US, Canadian and Israelis sites. The three time points for biopsy are

- Before initiation of therapy N= 40. This biopsy can be obtained after patient has signed consent for the study and within 14 days of start of protocol therapy.
- During therapy N=30; anticipated to be feasible in approx 75% of 40 patients. This biopsy is to be obtained between day 3-12 of cycle #2 or #3. This biopsy will occur around the time that the 2<sup>nd</sup> research blood draw is obtained. The timing of the second biopsy is not as important for participants on Arm B and can be obtained anytime during cycle #2 or cycle #3. Biopsies collected at this time outside of cycle #2 or #3 must be discussed with the MSK PI.
- At the time of progression of disease N= 30; anticipated to be feasible in approx 75% of the 24 patients. This biopsy can be obtained up to 28 days after the last dose of protocol therapy.

Four cores will be obtained at each biopsy where possible. The first core will be frozen in OCT, the second flash frozen in liquid nitrogen and the third/fourth core will be paraffin embedded.

For the research tissue analyses where adequate frozen tissue is available, frozen tissue will be preferentially used for sequencing. If adequate frozen tissue is not available, paraffin-embedded tissue will be utilized.

On and post treatment research biopsies are necessitated for (1) PAR levels following and during treatment, (3) sequencing for reversion mutation.

Biopsies will be tracked and monitored at the study sites using the SKI Freezer inventory system (SKIFI) which provides detailed real-time tracking information for all tissue samples obtained both at MSK and at collaborating institutions.

### **Research Biopsy Tissue specimens (archival and new procurements) should be sent to:**

Center for Pancreas Cancer Research (CPCR)  
Memorial Sloan Kettering Cancer Center  
Zuckerman Research Center

417 East 68<sup>th</sup> St., 8<sup>th</sup> Floor Rm. 853  
New York, NY 10065

**For specimens obtained at MSK new procurements will be processed by Tumor Procurement.**

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done  $\leq 4$  weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Patients are permitted to have a new cycle of therapy delayed up to 7 days for major life events (i.e. serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a deviation. Documentation to justify this delay should be provided.

### Study Calendar Arm A and Arm B (Part I)

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Treatment <sup>c</sup>
Veliparib (day 1-12 or longer)		A	A		A	A		A	A		A	A		
Gemcitabine, Cisplatin		A/B	A/B		A/B	A/B		A/B	A/B		A/B	A/B		
Informed consent	X													
Demographics	X													
Medical history	X				X			X			X			
Concurrent meds	X	X-----X												
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X			X			X			X			X
Performance status	X	X			X			X			X			X
CBC w/diff, platelets	X	X	X		X	X		X	X		X	X		X
Chemistry <sup>a</sup>	X	X*	X		X	X		X*	X		X	X		X*
EKG (within 6 weeks)	X													
Adverse event evaluation		X-----X												X
	X	Tumor measurements are repeated every 6 weeks +/- 5 days (Arm A, B). After 6 months on study, scans can be done every 9 weeks +/- 5 days. After 18 months on study, scans can be done every 12												X

Tumor measurements		weeks +/- 5 days. At the beginning of year 4, scans can be done every 16 weeks +/- 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												
Radiologic evaluation <sup>d</sup>	X	Radiologic measurements should be performed every 6 weeks +/- 5 days.												X
Medication Diary (Arm A)		X	X		X	X		X	X		X	X		X
B-HCG	X <sup>b</sup>													
Archived Tumor <sup>c</sup>	X													
Research Blood Draws <sup>e</sup>		X			Second research blood draw should be collected during days 3-12 of Cycle 2 or Cycle 3 (Week 4-5 or Week 7-8)									X
Image-guided biopsy <sup>g</sup> (Research)	X				Second image-guided biopsy should be obtained during days 3-12 of Cycle 2 or Cycle 3 <sup>g</sup> (Week 4-5 or Week 7-8)									X

Arm A: Lead-in portion of Part I: Veliparib + Gemcitabine + Cisplatin: Flat dose as assigned; po BID day 1-12 (or continuous dosing pending cohort). Days 1, 3 and 10 treatment and assessments, if applicable, can be adjusted +/- 48 hours.

Randomized Portion of Part I: Veliparib 80 mg PO BID day 1-12 q 3 weeks.

For Arm A, veliparib should start on Day 1 and chemotherapy should be administered on days 3 and 10. Days 1, 3 and 10 can be adjusted +/- 48 hours.

Arm B: Gemcitabine, Cisplatin IV days 3 and 10 (+/- 48 hours) q 3 weeks. For Arm B, a separate Day 1 is not required; Day 1 and Day 3 procedures can be combined.

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium, phosphorus. To be obtained within 0-2 days of day 1 of the start of each cycle to begin taking Veliparib. Creatinine must be obtained within 48 hours of day 10 dosing (optional full chemistry panel, magnesium, phosphorus on week 2 of each cycle).

\*CEA, Ca 19-9 will be drawn at the start of every odd cycle of therapy, e.g., cycle 1, 3, 5, etc., and at end of therapy. If the start of a cycle is delayed, CEA and CA19-9 are not required to be repeated.

b: Blood or urine pregnancy test (women of childbearing potential).

c: Off-treatment evaluation within 30 days of last treatment. Refer to [section 5.6](#) for duration of follow up.

d: CT scan with contrast of the chest, abdomen, pelvis preferable. MRI abdomen/pelvis with contrast may be performed in situations where a CT scan is contra-indicated. A non-contrast chest CT should be performed for patients requiring an MRI of the abdomen/pelvis. (See [section 5.4](#))  
Imaging to be performed every 6 weeks +/- 5 days. After 6 months on study, scans can be done every 9 weeks +/- 5 days. After 18 months on study, scans can be done every 12 weeks +/- 5 days. Patients randomized to Arm A who continue on single-agent veliparib per Arm C dosing schedule will have a scan every 8 weeks +/- 5 days for the first 2 scans, then every 12 weeks +/- 5 days. At the beginning of year 4, scans can be done every 16 weeks +/- 8 weeks.

e: Where possible archived tumor tissue will be obtained on all patients (see [section 9.1.3](#)).

f: Research blood draws will be obtained as per [section 9.1.2.1](#). Obtained pre-treatment, on treatment during cycle #2 or #3 (days 3-12 of either cycle) and at of treatment assessments (or within 28 days of the last dose of study therapy).

g: Research tumor biopsies are to be obtained pre-treatment, on treatment ARM A: To be obtained between days 3-12 of cycle #2 or cycle #3. ARM B: To be obtained anytime during cycle #2 or cycle #3. and at progression of disease (where possible). Patients will not undergo biopsy if it poses a safety risk to the patient or delays treatment unnecessarily. (See [section 9.1.3](#))

**Patients who are enrolled on the lead-in, non-randomized portion of Part I (initial 6-12 patients), no new research biopsies or blood samples will be obtained. Archival tumor specimens will be requested on these patients.**

### **Study Calendar Arm C (Part II)**

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Treatment <sup>c</sup>
Veliparib (day 1-28)		A	A	A	A	A	A	A	A	A	A	A	A	
Medication Diary		X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent	X													
Demographics	X													
Medical history/ Update	X			X		X				X				
Concurrent meds	X	X-----X												X
Physical exam	X	X		X		X				X				X
Vital signs	X	X		X		X				X				X
Height	X													
Weight	X	X		X		X				X				X
Performance status	X	X		X		X				X				X
CBC w/diff, platelets	X	X				X				X				X
chemistry <sup>a</sup>	X	X*				X				X*				X*
EKG (within 6 weeks)	X													
Adverse event evaluation		X-----X												X
Tumor measurements	X	Tumor measurements are repeated every 8 weeks +/- 5 days in Arm C. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation <sup>d</sup>	X	Radiologic measurements should be performed every 3 – 6 months +/- 2 weeks.												X
B-HCG	X <sup>b</sup>													
Archived Tumor <sup>e</sup>	X													

Arm C Veliparib: Dose as assigned; PO BID day 1-28 continuously. Day 1 treatment and assessments can be adjusted +/- 72 hours.

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, phosphorus. To be obtained within 0-2 days of day 1 of each cycle.

\*Ca 19-9, CEA will be drawn every 8 weeks.

b: Blood or urine pregnancy test (women of childbearing potential).

c: Off-treatment evaluations. Refer to [section 5.6](#) for duration of follow up. Patients on Part II/Arm C will be strongly encouraged to return for the end of treatment visit, however, missed visits due to progression of disease, very long distance from center etc., will not be considered violations.

d: CT scan with contrast of the chest, abdomen, pelvis preferable. MRI abdomen/pelvis with contrast may be performed in situations where a CT scan is contra-indicated. A non-contrast chest CT should be performed for

patients requiring an MRI of the abdomen/pelvis. See [section 5.4](#).  
Imaging to be performed every 3 – 6 months +/- 2 weeks, pending clinical status / tumor markers.  
e: Where possible archived tumor tissue will be obtained on all patients (see [section 9.1.3](#)).

**Telemedicine visits will be permitted as an alternate to inperson visits where clinically appropriate.**

## 11. MEASUREMENT OF EFFECT

Tumor response is the primary endpoint of this trial and patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 6 weeks (Arm A and B) and every 8 weeks for Arm C.

### 11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated every 6 weeks +/- 5 days (Arm A and B) and every 8 weeks +/- 5 days for Arm C irrespective of treatment delays. For Arms A and B, after 6 months on study, scans can be done every 9 weeks +/- 5 days. After 18 months on study, scans can be done every 12 weeks +/- 5 days. Patients randomized to Arm A who continue on single-agent veliparib per Arm C dosing schedule will have a scan every 8 weeks +/- 5 days for the first 2 scans, then every 12 weeks +/- 5 days. At the beginning of year 4, scans can be done every 16 weeks +/- 8 weeks. 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) [*Eur J Ca* 45:228-247, 2009]. 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.

#### 11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of first dose of any medication in Arm A, B and C.

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.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Patients who are evaluable for toxicity only or without response assessments during the first cycle of therapy (deemed inevaluable for response) may be replaced.

#### 11.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area are not considered as measurable disease.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  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.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as

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

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

#### 11.1.3 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 4 weeks before the beginning of the treatment.

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

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

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

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

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

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

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

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

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the

Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

#### 11.1.4 Response Criteria

##### 11.1.4.1 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 diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

##### 11.1.4.2 Evaluation of Non-Target Lesions

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

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

clinical response.

**Non-CR/Non-PD:**

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

**Progressive Disease (PD):**

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

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

11.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** Only for non-randomized trials with response as primary endpoint.</p> <p>*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><b>Note:</b> 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 “<i>symptomatic deterioration.</i>” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

#### 11.1.5 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 progressive 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, including the baseline measurements.

#### 11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

#### 11.1.7 Response Review

Response review will be conducted as per [Section 13](#).

## 12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in [Section 7](#). (Adverse Events: List and Reporting Requirements).

## 12.1 Responsibility for Data Submission

MSK will assign a CRC and RPC to manage data entry for this study. The CRC and RPC will enter data into a secure database (CRDB) for MSK and outside patients respectively. MSK is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator review.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site ([http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/cdus.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/cdus.htm)).

**Note:** All adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via the monitoring method identified above.

### 12.1.1 Data and Source Documentation for Participating Sites Data

Standardized Case Report Forms (CRF's), directions for use and sign off requirements have been generated for this study. A schedule of required forms is shown [below](#). Participating sites will be responsible for filling out these CRFs and submitting them to MSK per the designated timelines. MSK staff will enter the data into a secure database (Clinical Research Database – CRDB) to facilitate CDUS transfer.

Research staff at MSK will review data as it is submitted. In the event of inconsistent or missing data, queries will be sent by MSK Research staff to the participating sites.

#### Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. All source documentation must be translated into English prior to submission to MSK. Relevant source documentation to be submitted to the MSK study coordinator throughout the study includes:

- Baseline measures to assess pre-protocol disease status (ex. CT, Pathology Report)
- Treatment Records
- Grade 3-5 Toxicities/Adverse Events not previously submitted with SAE Reports
- Response Designation

Source documentation must include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

For non-N01 contract holders, at the time of electronic data/CRF submission, source documentation (translated into English) relevant to eligibility, treatment, outcome and SAEs should be submitted to MSK. This source will be reviewed against the data as it is entered.

Data and source documentation to support data should be transmitted to MSK according to chart [below](#):

	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	SAE	Off Treatment
SUBMISSION SCHEDULE							
Source Documentation	Within 24 hours	within 14 days of visit				Within 3 days of event; updates to be submitted as available	Within 14 days of visit
CRFs	Within 7 days of visit						
Required Forms							
Demographics Form	X						
Medical History Form	X						
Concomitant Medications Form	X	X	X	X	X		X
Physical Exam Form	X	X	X	X	X		X
Treatment Form		X	X	X	X		X
Laboratory Form	X	X	X	X	X		X
Lesion/EOD Form					X		X
Adverse Event Form		X	X	X	X	X	X
Serious Adverse Event Form						X	

Research staff at MSK will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating site. Queries will be sent by MSK Research staff as often as needed. Participating sites should respond to data queries within 14 days of receipt.

## 12.2 CTEP Multicenter Guidelines

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

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.
- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO ([PIO@ctep.nci.nih.gov](mailto:PIO@ctep.nci.nih.gov)) except for Group studies.

### **12.3 Quality Assurance**

Monthly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits may be conducted by the study team.

#### **12.3.1 Quality Assurance of Participating Sites**

Quality Assurance will be conducted according to MSK guidelines and Multicenter SOPs.

Research staff at MSK will conduct periodic reviews of regulatory documentation, protocol compliance and data, and issue queries as appropriate. The level and frequency of monitoring or auditing may be adjusted based on ongoing site performance.

#### **12.3.2 Response Review**

Since therapeutic efficacy is a stated primary objective, all sites participant's responses are subject to review by MSK's Therapeutic Response Review Committee (TRRC). Radiology, additional laboratory reports will need to be obtained from the participating sites for MSK TRRC review and confirmation of response assessment. These materials must be sent to MSK promptly upon request.

### **12.4 Data and Safety Monitoring**

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials," which can be found at: <http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1>. The

DSM Plans at MSK were established and are monitored by the Clinical Research Administration. The MSK DSM Plans can be found on the MSK Intranet at: <http://onemsk/clinresearch/Documents/MSKCC Data and Safety Monitoring Plans.pdf>

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g. Protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

For Multicenter studies, standardized Case Report Forms (CRFs) have been generated from this study that meets the requirements of CTEP and MSK data reporting. A set of CRFs will be sent to each center (for photocopying and use) following local activation

## **12.5 Regulatory Documentation**

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document. Prior to implementing this protocol at the participating sites, approval for the MSK IRB/PB approved protocol must be obtained from the participating site's IRB and submitted to the CTEP PIO.

The following documents must be provided to MSK before the participating site can be initiated and begin enrolling participants:

### For N01/U01 contract holders and their affiliates

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form and HIPAA authorization

### For non N01 contract holders

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization

- Participating Site IRB approved consent form and HIPAA authorization
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSK will formally contact the site and grant permission to proceed with enrollment.

Participating sites that are consulting and/or conducting specimen or data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

#### 12.5.1 Amendments

Each change to the protocol document must be organized and documented by MSK and approved first by the MSK IRB/PB. Protocol amendments that affect MSK only (e.g. change in MSK Co-Investigator, MSK translation, etc.) do not require IRB review at the participating site(s). All other protocol amendments will be immediately distributed to each participating site upon receipt of MSK IRB/PB approval.

Each participating site must obtain approval for all amendments within 90 calendar days of receipt of the amended MSK IRB/PB approved documents. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, participating sites will not be permitted to continue enrolling new participants until site IRB approval of the revised protocol documents is granted and submitted to MSK.

##### 12.5.1.1 Site-Initiated Amendments/Modifications

Participating sites must notify MSK research staff of any site-initiated amendments/modifications. Each participating site must provide all site IRB approvals for amendments/modifications and the most current approved version of the site informed consent form and HIPAA authorization at the time of approval. Documents must be submitted to MSK on a continuing basis.

#### 12.5.2 Additional IRB Correspondence

##### **Continuing Review Approval**

The Continuing Review Approval letter from each participating site's IRB and the most current approved version of the informed consent form must be submitted to MSK within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant enrollment.

##### **Deviations**

A protocol deviation on this study is defined as any incident involving non-adherence to

an IRB approved protocol. Deviations typically do not have a significant effect on the rights, safety, or welfare of research participants or on the integrity of the resultant data. Deviations that represent unanticipated problems involving risks to participants or others, or serious adverse events should be reported according to sections [7.6](#) and [7.7](#) of this protocol.

CTEP will not issue or approve any waivers for protocol deviations; therefore, prospective deviations may not be submitted to the MSK IRB/PB for approval. An anticipated need for a change or departure from this protocol should be discussed with the medical monitor, appropriately acknowledged and documented in the patient's medical record. Instances of non-adherence, anticipated or otherwise, must then be reported to the MSK IRB/PB as a retrospective deviation.

Deviations that do not adversely affect the rights and/or welfare of the participant or the scientific validity of the study and are related to protocol scheduling changes outside of the allowed window due to a holiday (e.g., New Year's, Thanksgiving, etc.) and/or inclement weather or other natural event do not require reporting to the MSK IRB/PB. However, they must be clearly documented in the patient's medical record.

#### *Participating Site IRB Reporting*

Participating sites should report all deviations to their institution's IRB per local guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations should be submitted to MSK upon receipt.

#### **Other correspondence**

Participating sites should submit all other correspondence to their institution's IRB according to local guidelines, and submit copies of official site IRB correspondence, including approvals and acknowledgements to MSK.

#### **12.5.3 Document Maintenance**

The MSK PI and participating site PI will maintain adequate and accurate records to fully document protocol implementation and allow data to be subsequently verified.

The participating sites will ensure that all regulatory documents and participating site IRB correspondence are maintained in an on-site regulatory binder and sent to MSK as outlined within this addendum. The on-site regulatory binder will be reviewed by the designated study monitor at monitoring visits. A regulatory binder for each participating site will also be maintained at MSK within the institution's Protocol Information Management System (PIMS). After study closure, the participating sites must maintain all source documents, study related documents and CRFs for 3 years.

### **12.6 Noncompliance**

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld (if applicable), until the

outstanding issues have been resolved.

### **12.7 Ethical and Administrative Issues**

The Investigator will agree to personally conduct and supervise the proposed investigations according to recognized principles of good clinical practice (GCP).

### **12.8 Institutional Review Board Approval**

This protocol and the informed consent will be reviewed and approved by the IRB before the study is initiated. The Investigator is then responsible for informing the IRB of the completion of the study and will provide the IRB a final study status report. The Investigator/Study Coordinator will inform the IRB of all serious adverse events.

### **12.9 NCI/ DCTD Standard Language/ CRADA**

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
  - a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
  - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the

clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

- c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator ([http://ctep.cancer.gov/industryCollaborations2/intellectual\\_property.htm](http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm)). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: [ncicteppubs@mail.nih.gov](mailto:ncicteppubs@mail.nih.gov)

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

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Study Design/Endpoints

There are two clinical trials under NCI #8993.

**Part I:** Randomized, phase II trial of gemcitabine, cisplatin and veliparib (Arm A) or gemcitabine, cisplatin (Arm B) in patients with untreated locally advanced or metastatic BRCA or PALB2-mutated pancreas adenocarcinoma. The randomized phase II trial is non-blinded and open-label with a Simon two-stage design in each study arm.

The initial 6-24 patients enrolled in Part I will NOT be randomized. These patients (either known or possible BRCA or PALB2 mutation) will be treated as part of the lead-in, non-randomized portion of the study exploring 4 dose levels of veliparib: 20 mg PO BID day 1-12 (dose level 0), 40 mg PO BID day 1-12 (dose level 1) 80 mg po BID day 1-12 (dose level 2), 80 mg po BID day 1- 21 (continuous) (dose level 2A, 140 mg po BID day 1-21 (dose level 3) and 200 mg po BID day 1-21 (dose level 4), in conjunction with gemcitabine 600 mg/m<sup>2</sup> and cisplatin 25 mg/m<sup>2</sup> IV both on day 3 and 10 of a 3-week cycle.

Following finalization of the veliparib dosing, subsequent patients will be randomized on a 1:1 basis to either gemcitabine, cisplatin and veliparib (Arm A) or gemcitabine and cisplatin (Arm B). All assignments and doses will be evident to physicians, study personnel and patients. Randomization determinations will be coordinated by the Clinical Research Administration Office at MSK.

**Part II:** Single-agent veliparib (Arm C) in patients with previously treated locally advanced or metastatic BRCA or PALB2-mutated pancreas adenocarcinoma.

There will be no randomization in Part II. The study design for Part II is a single-arm, open-label, non-randomized, Simon two-stage design.

### 13.2 Sample Size/Accrual Rate

The total enrollment to these studies (Arm A, B and C) will be between 53 and 107 patients.

For **Part I (Arm A and B):**

6-24 patients will be recruited to the non-randomized, lead-in portion of Part I.

16-25 patients will be recruited to study Arm A (Gemcitabine, cisplatin, and veliparib) and 16-25 study Arm B (Gemcitabine, cisplatin).

Enrollment for Part I: Min 32 – max 50.

For **Part II (Arm C)**: 15-33 patients will be recruited to study Arm C (Veliparib).  
Enrollment for Part II: Min 15 – max 33.

For both Part I and II, we anticipate total enrollment of 2-3 patients per month. Total time for study recruitment: 36-42 months. Please see also [section 13.4](#) below.

### 13.3 Stratification Factors

None planned.

### 13.4 Analysis of Endpoints

#### **Primary Endpoint (Part I):**

In **Part I**, patients with a BRCA or PALB2 mutation will be randomized to one of two arms: patients in Arm A will receive gemcitabine, cisplatin and veliparib. Patients in Arm B will receive gemcitabine and cisplatin.

Patients treated on the non-randomized lead-in portion of the study will be used to optimize the dosing of veliparib with gemcitabine and cisplatin.

Primary Endpoint Non-Randomized portion (Part I): To determine the optimal dose of veliparib with gemcitabine and cisplatin.

Dose levels of veliparib of 20 mg po BID (dose level 0), 40 mg po BID (dose level 1), and 80 mg po BID (dose level 2), all dosed day 1-12, will be assessed. If no DLT is observed then further dose levels will be evaluated as follows: dose level 2A: 80 mg day 1-21 (continuous dosing of veliparib); dose level 3: 140 mg PO BID day 1-21; dose level 4: 200 mg po BID day 1-21. See [Section 5.1](#).

If a maximum of 1/3 or 1/6 experience a DLT at 20 mg BID, the dose of veliparib will increase to 40 mg BID, and so forth. If 2/3 or 2/6 experience a DLT, the dose level to be evaluated in the trial will be the next lowest dose level of veliparib.

As of 12/13/13, the veliparib dose for Arm A of the randomized portion of Part I has been finalized at 80 mg PO BID day 1-12, q 3 weeks.

As of 01/16/15, the Phase II Single Arm Study of Single-Agent Veliparib (Part II) has been closed to accrual.

#### **Primary Endpoint Randomized portion (Part I):**

To evaluate the response rate (RECIST 1.1) of gemcitabine, cisplatin and veliparib (Arm A) and gemcitabine and cisplatin (Arm B) in BRCA/PALB2 carriers with advanced pancreas adenocarcinoma.

Simon's two-stage minimax design will be employed separately in each arm A and B. Assuming an unacceptable response rate of 10% and a promising rate of 30% with

type I and II error rates of 10% each. Of note, there are no reference data to draw upon to guide where the benchmark should be set for the lower margin of activity for gemcitabine and cisplatin in BRCA or PALB2 mutated pancreas adenocarcinoma. The investigators have chosen a 10% response rate based on activity of single agent gemcitabine in sporadic pancreas adenocarcinoma (Burris, et al, J Clin Oncol, 1997). Activity below 10% would be of no interest.

In each arm, 16 patients will be enrolled in the first stage. If 1 or less responses are observed in a particular arm, accrual for that arm will be stopped and the regimen in that arm will be considered not worthy of further investigation. If 2 or more responses are observed, an additional 9 patients will be accrued for a total of 25 patients. If 5 or more of the 25 patients in one arm achieve a response then the regimen in that arm will be worthy of further investigation. The probability of early termination is 0.51.

In the event that both arms show promising activity at the end of the second stage, we propose enrolling an additional 10 patients in each arm for a total of 35 patients in each arm A and B. This would allow us to distinguish between true response rates of 20% and 40% with 83% power at the 1-sided 0.17 significance level, or between true response rates of 30% and 50% with 79% power at the 1-sided 0.16 level. These power calculations were conditioned on the successful completion of the Simon's two stage design in both arms. If both arms show promising activity at the end of the second stage, the comparison between the two arms will also be conditioned on the successful completion of the Simon's two stage design. A discussion with CTEP and a study amendment will be required for this part of the study to proceed. In this latter scenario the study recruitment for Part I will be expanded to a total N= 70.

#### Recruitment for Part I:

An initial 6-24 patients will be accrued in a non-randomized fashion to determine the optimal dose of veliparib combined with gemcitabine and cisplatin.

For the randomized portion of Part I: Planned 32-50 patients. If accrual is slower than anticipated, then the control arm of gemcitabine and cisplatin (Arm B) will close for poor accrual and only the combination in Arm A will be evaluated. A discussion with CTEP and study amendment will be required for this part of the study to proceed. In this latter scenario the study recruitment for Part I will be condensed to total N= 25 for Arm A.

#### Primary Endpoint (Part II):

In **Part II** of this study the efficacy of single-agent veliparib (Arm C) in patients that who have already received prior therapy but without prior receipt of a PARP inhibitor for locally advanced or metastatic pancreas adenocarcinoma will be established.

#### Primary Endpoint (Part II):

To evaluate the response rate (RECIST criteria) of single-agent veliparib (Arm C) in BRCA/ PALB2 carriers with previously treated pancreas adenocarcinoma.

Patients will be eligible for Part II if they are enrolled on Arm B of Part I

(gemcitabine, cisplatin arm) and subsequently meet the eligibility criteria for Part II. Patients will also be eligible independently provided the eligibility criteria in [Section 3](#) are met.

Simon's two-stage optimal design will be employed. Assuming an unacceptable response rate of 10% and a promising rate of 28% with type I and II error rates of 10% each. Similar to part I, there are no reference data to draw upon to guide the lower boundary of activity in a previously treated pancreas cancer population and specifically not in a BRCA/PALB2 mutated pancreas population. We have chosen 10% as the lower boundary of activity as a level of activity below which would hold no interest. This involves enrolling 15 patients in the first stage and if 2 or more responses are observed then further enrolling 18 patients for a total of 33 patients. At the end of the second stage if 6 or more patients respond then veliparib as single agent will be considered worthy of further investigation.

As veliparib single-agent will be given as salvage therapy after patients progress on cisplatin and gemcitabine, the accrual to this part of the study will proceed as follows: If Arm B (Part I) stops after stage I, up to 15 patients enrolled in the first stage of Arm B (on progression of their disease) will be potentially eligible for Arm C. If there are 2 or more responders after switching to veliparib then an additional 18 patients will be enrolled and evaluated as described above. If Arm B is not terminated early, then patients will be eligible to participate in Arm C in Part II of the study as they progress on chemotherapy in Arm B. All patients enrolled to Arm B will be offered veliparib, if eligible, when they progress on chemotherapy alone. As of 01/16/2015, this option is no longer available.

Recruitment for part II: Minimum 15 (some patients may accrue from Part I) - maximum 33.

To facilitate recruitment to Part II of the study, patients with pancreas cancer with a known BRCA 1, 2 or PALB2 mutation and who have been previously treated (and hence not eligible for part I of the study) and who have not previously received a PARP inhibitor, will be eligible.

For the primary study endpoint for Part I and Part II, in view of national and international site involvement, the study will not be stopped after enrollment of the initial number of patients for each stage assessment. However, if the decision to expand has not already been made by the end of stage I, this decision will be made as soon as feasible following completion of recruitment to stage I.

All imaging must be submitted to MSK as per [Section 5.4](#).

### **Secondary Endpoints**

#### **Part I:**

- To evaluate progression-free survival in study Arm A and study Arm B.
- To describe the safety and tolerability of gemcitabine, cisplatin and veliparib

(Arm A) and gemcitabine and cisplatin (Arm B) in BRCA/ PALB2 carriers with advanced pancreas adenocarcinoma.

- To determine the disease control rate (CR + PR + SD) and duration of response in study Arm A and Arm B.
- To evaluate overall survival in study Arm A and Arm B.

#### **Part II:**

- To evaluate progression-free survival for single-agent veliparib in BRCA/ PALB2 carriers with previously treated pancreas adenocarcinoma (Arm C).
- To describe the safety and tolerability of single-agent veliparib in BRCA carriers with carriers with previously treated pancreas adenocarcinoma.
- To determine the disease control rate (CR + PR + SD) and duration of response in Arm C.
- To evaluate overall survival in Arm C.

#### Progression-Free Survival and Overall Survival

Progression-free survival and overall survival will be estimated using the Kaplan-Meier method. The progression-free survival will be determined as being the time elapsed from the date of study enrollment to documentation of clear-cut progression of disease or last follow-up. Overall survival is dated from the time of study enrollment to the date of death or last follow-up.

#### Disease Control Rate

The disease control rate, DCR, is the complete response rate plus the partial response rate plus the rate of patients with stabilized disease, or  $DCR = CR + PR + SD$ . The DCR will be recorded for all three study arms.

#### Toxicity/Safety Monitoring

We expect all three arms of the study to be well-tolerated. Toxicity and tolerability of all three study arms will be assessed and summarized using descriptive statistics. The safety analyses will be performed on all patients who received any dose of therapy.

Adverse events will be described using the NCI CTCAE v4.0 criteria (<http://ctep.cancer.gov/>). Serious adverse events will be summarized, including a causality assessment.

Frequency and severity of adverse events according to the NCI CTCAE v4.0 body system and severity criteria will be described. In addition, frequency of Grade 3 or 4 adverse events will be described separately. Causality will also be noted.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting beginning April 1, 2018 (investigators may continue to collect and locally store AE data in CTCAE v4.0).

The number of treatment cycles administered will be summarized using descriptive

statistics. Treatment delays will be summarized using counts and percentages.

### **Correlative Studies Endpoints**

#### **Aim 1**

Tumor biopsy correlates will be available from approximately N= 24 patients enrolled in Arms A and B (Part I). Descriptive statistics will be utilized to describe the molecular and genetic phenotype of these tumors along with the clinical and epidemiologic characteristics of these patients. An exploratory analysis will be undertaken to correlate the molecular profiling with outcome (e.g., response, progression-free survival time, overall survival time). Kaplan-Meier plots and Cox regression will be used for exploratory analysis of the survival endpoints and logistic regression will be used for response endpoints. This analysis will be used to assess for baseline characteristics that impact clinical benefit and allow a search for specific markers that may predict for benefit. Patients who experience an objective response will be compared to those that did not – in terms of baseline correlates and demographics, in order to try and understand the lack of activity.

#### **Aim 2**

Identification of possible BRCA reversion mutations which may restore homologous repair function and correlate with resistance to therapy will be undertaken. The presence of such mutations have not previously been reported in pancreas adenocarcinoma and thus we do not know whether or not any will be identified. For the purposes of this analysis the evaluation will be a descriptive and exploratory one. Identification of BRCA reversion mutations would be a novel observation in pancreas adenocarcinoma and will provide insight into mechanisms of resistance. The proportion of genetic reversions of BRCA gene mutations to wild type will be summarized using binomial proportions.

#### **Aim 3**

Analysis of peripheral blood mononuclear cells (PBMC's): It is hypothesized that baseline PAR inhibition will predict for response. As a result patients will be pooled in a multivariate logistic regression evaluating response as a function of PAR inhibition and gemcitabine/cisplatin +/- veliparib. We will also evaluate the role of PAR inhibition on the response rate for Arm A.

Patients with BRCA and PALB2 mutations may have impaired repair and it is possible that baseline PAR levels may be elevated. Previous publications have reported a median PAR level of 99 pg/ml with a standard deviation of 217 pg/ml in non-BRCA related carriers. This large variability limits the power to detect a baseline difference between non- BRCA and BRCA/PALB2 carriers. Change in PAR levels will be summarized by percent of baseline.

Analysis of changes in correlatives (blood) for each arm. A minimum of 16 (and up to 25) patient samples will be obtained for each arm of the study. Blood will be evaluated for change due to treatment. In each arm, a paired-t test will be employed to compare baseline to after treatment PAR levels. Standard descriptive methods will

be used to summarize baseline levels and the changes from baseline (following treatment). Changes in PAR levels from baseline to after treatment will be associated with response using Wilcoxon rank sum test.

Where possible, paired biopsy samples (prior to treatment and at progression) will be obtained for up to 20 patients on arm A and B (N=40 total patients). Please see detailed description of correlative studies in section 9. These biopsies will be evaluated in an exploratory fashion to assess for activity specific to veliparib is identified in tumor tissue and if these findings relate to baseline measurements and can help distinguish between responders and non-responders in this small sample size.

We will evaluate the difference in  $\gamma$ H2AX between the gemcitabine, cisplatin and veliparib (arm A) and the gemcitabine, cisplatin arm (arm B) in the tumor biopsies. For each of the post treatment time points, changes from baseline in  $\gamma$ H2AX levels will be compared between the two arms using Wilcoxon rank sum test. Comparison of PAR levels and  $\gamma$ H2AX levels in individual patients will be made

#### **Aim 4 (Exploratory Aims)**

Descriptive statistics will be employed to describe the observed effects. Use of response and survival endpoints will all be evaluated in an exploratory fashion. Given sample size constraints the purposes here are toward hypothesis identification for future studies. Transcriptome analyses by RNAseq will be processed in the Genomics Core Laboratory under the direction of Agnes Viale and in the MSK Bioinformatics Core Facility. Further analysis will be performed on log2-transformed data will be studied using tools in R statistical language (e.g. t-test and limma package). Differentially expressed genes between prior and during treatment will be found using the limma package, and standard cut-offs (False Discovery Rate up to 25% and fold-change cut-off=2).

## **14. PROTECTION OF HUMAN SUBJECTS**

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Memorial Sloan Kettering Cancer Center has filed forms HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both male and female, will be accepted into the protocol. .

Exclusion of Lactating or Pregnant Women: Children have been excluded from this study. Pancreatic adenocarcinoma is an adult cancer. Thus, the relevance of this drug to the pediatric population has not been established. Lactating and pregnant women are also excluded because of potential anti-proliferative effects of chemotherapy that may be harmful to the developing fetus or nursing infant.

Benefits: It is possible that this treatment will result in shrinkage of pancreatic cancer or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including, CT or MRI scans, all drug administration fees and all hospitalizations, even for complications of treatment. Veliparib will be supplied by CTEP. Patients will not be responsible for the costs of blood or tissue procurement obtained for research purposes.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: For patients with advanced pancreatic cancer, alternative treatments may include other chemotherapy regimens. Patients may be eligible for other investigational studies.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (eg, qualified monitors from MSK or collaborating institutions, CTEP, NCI.), may review patients records and pathology slides, as required.

#### **14.1 Privacy**

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

### **15. INFORMED CONSENT PROCEDURES**

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

#### *For Participating Sites*

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to Good Clinical Practice and protocol guidelines.

A note will be placed in the participant's medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

## 16. REFERENCES

1. Ame JC, Spenlehauer C, de Murcia G. The PARP superfamily. *Bioessays*. 2004; **26**(8): 882-93.
2. Tomoda T, Kurashige T, Moriki T, Yamamoto H, Fujimoto S, Taniguchi T. Enhanced expression of poly(ADP-ribose) synthetase gene in malignant lymphoma. *Am J Hematol*. 1991; **37**(4): 223-7.
3. Shiobara M, Miyazaki M, Ito H, Togawa A, Nakajima N, Nomura F, et al. Enhanced polyadenosine diphosphate-ribosylation in cirrhotic liver and carcinoma tissues in patients with hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2001; **16**(3): 338-44.
4. Fukushima M, Kuzuya K, Ota K, Ikai K. Poly(ADP-ribose) synthesis in human cervical cancer cell-diagnostic cytological usefulness. *Cancer Lett*. 1981; **14**(3): 227-36.
5. Alderson T. New targets for cancer chemotherapy--poly(ADP-ribosylation) processing and polyisoprene metabolism. *Biol Rev Camb Philos Soc*. 1990; **65**(4): 623-41.
6. Wielckens K, Garbrecht M, Kittler M, Hilz H. ADP-ribosylation of nuclear proteins in normal lymphocytes and in low-grade malignant non-Hodgkin lymphoma cells. *Eur J Biochem*. 1980; **104**(1): 279-87.
7. Berger NA, Adams JW, Sikorski GW, Petzold SJ, Shearer WT. Synthesis of DNA and poly(adenosine diphosphate ribose) in normal and chronic lymphocytic leukemia lymphocytes. *J Clin Invest*. 1978; **62**(1): 111-8.
8. Hirai K, Ueda K, Hayaishi O. Aberration of poly(adenosine diphosphate-ribose) metabolism in human colon adenomatous polyps and cancers. *Cancer Res*. 1983; **43**(7): 3441-6.
9. Fernet M, Ponette V, Deniaud-Alexandre E, de Murcia JM, de Murcia G, Giocanti N, et al. Poly(ADP-ribose) polymerase, a major determinant of early cell response to ionizing radiation. *Int J Radiat Biol*. 2000; **76**(12): 1621-9.
10. Shall S, de Murcia G. Poly(ADP-ribose) polymerase-1: what have we learned from the deficient mouse model? *Mutat Res*. 2000; **460**(1): 1-15.
11. Masutani M, Nozaki T, Nakamoto K, Nakagama H, Suzuki H, Kusuoka O, et al. The response of Parp knockout mice against DNA damaging agents. *Mutat Res*. 2000; **462**(2-3): 159-66.
12. Ame JC, Rolli V, Schreiber V, Niedergang C, Apiou F, Decker P, et al. PARP-2, A novel mammalian DNA damage-dependent poly(ADP-ribose) polymerase. *J Biol Chem*. 1999; **274**(25): 17860-8.
13. Menissier de Murcia J, Ricoul M, Tartier L, Niedergang C, Huber A, Dantzer F, et al. Functional interaction between PARP-1 and PARP-2 in chromosome stability and embryonic development in mouse. *Embo J*. 2003; **22**(9): 2255-63.
14. Schreiber V, Ame JC, Dolle P, Schultz I, Rinaldi B, Fraulob V, et al. Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1. *J Biol Chem*. 2002; **277**(25): 23028-36.
15. Johansson M. A human poly(ADP-ribose) polymerase gene family (ADPRTL): cDNA cloning of two novel poly(ADP-ribose) polymerase homologues. *Genomics*. 1999; **57**(3): 442-5.
16. Yu SW, Wang H, Poitras MF, Coombs C, Bowers WJ, Federoff HJ, et al. Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor. *Science*. 2002; **297**(5579): 259-63.
17. D'Amours D, Sallmann FR, Dixit VM, Poirier GG. Gain-of-function of poly(ADP-ribose) polymerase-1 upon cleavage by apoptotic proteases: implications for apoptosis. *J Cell Sci*. 2001; **114**(Pt 20): 3771-8.
18. Memisoglu A, Samson L. Base excision repair in yeast and mammals. *Mutat Res*. 2000; **451**(1-2): 39-51.
19. Ruscetti T, Lehnert BE, Halbrook J, Le Trong H, Hoekstra MF, Chen DJ, et al. Stimulation of the DNA-dependent protein kinase by poly(ADP-ribose) polymerase. *J Biol Chem*. 1998; **273**(23): 14461-7.
20. Galande S, Kohwi-Shigematsu T. Poly(ADP-ribose) polymerase and Ku autoantigen form a complex and synergistically bind to matrix attachment sequences. *J Biol Chem*. 1999; **274**(29): 20521-8.
21. Boulton S, Kyle S, Durkacz BW. Interactive effects of inhibitors of poly(ADP-ribose) polymerase and DNA-dependent protein kinase on cellular responses to DNA damage. *Carcinogenesis*. 1999; **20**(2): 199-203.
22. Liu L, Taverna P, Whitacre CM, Chatterjee S, Gerson SL. Pharmacologic disruption of base excision repair sensitizes mismatch repair-deficient and -proficient colon cancer cells to methylating agents. *Clin Cancer Res*. 1999; **5**(10): 2908-17.
23. Jagtap P, Szabo C. Poly(ADP-ribose) polymerase and the therapeutic effects of its inhibitors. *Nat Rev Drug Discov*. 2005; **4**(5): 421-40.
24. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005; **434**(7035): 913-7.
25. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005; **434**(7035): 917-21.
26. Masutani M, Suzuki H, Kamada N, Watanabe M, Ueda O, Nozaki T, et al. Poly(ADP-ribose) polymerase gene disruption conferred mice resistant to streptozotocin-induced diabetes. *Proc Natl Acad Sci U S A*. 1999; **96**(5):

- 2301-4.
27. de Murcia JM, Niedergang C, Trucco C, Ricoul M, Dutrillaux B, Mark M, et al. Requirement of poly(ADP-ribose) polymerase in recovery from DNA damage in mice and in cells. *Proc Natl Acad Sci U S A*. 1997; **94**(14): 7303-7.
  28. Veuger SJ, Curtin NJ, Richardson CJ, Smith GC, Durkacz BW. Radiosensitization and DNA repair inhibition by the combined use of novel inhibitors of DNA-dependent protein kinase and poly(ADP-ribose) polymerase-1. *Cancer Res*. 2003; **63**(18): 6008-15.
  29. Brock WA, Milas L, Bergh S, Lo R, Szabo C, Mason KA. Radiosensitization of human and rodent cell lines by INO-1001, a novel inhibitor of poly(ADP-ribose) polymerase. *Cancer Lett*. 2004; **205**(2): 155-60.
  30. Calabrese CR, Almassy R, Barton S, Batey MA, Calvert AH, Canan-Koch S, et al. Anticancer chemosensitization and radiosensitization by the novel poly(ADP-ribose) polymerase-1 inhibitor AG14361. *J Natl Cancer Inst*. 2004; **96**(1): 56-67.
  31. Obach RS, Baxter JG, Liston TE, Silber BM, Jones BC, MacIntyre F, et al. The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism data. *J Pharmacol Exp Ther*. 1997; **283**(1): 46-58.
  32. Jemal A, Siegel R, Xu J, Ward E. *Cancer Statistics, 2010*. *CA Cancer J Clin*. 2010.
  33. Ghaneh P, Costello E, Neoptolemos JP. Biology and management of pancreatic cancer. *Gut*. 2007; **56**(8): 1134-52.
  34. Hruban RH, Goggins M, Kern SE. Molecular genetics and related developments in pancreatic cancer. *Current opinion in gastroenterology*. 1999; **15**(5): 404-9.
  35. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Madiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *Journal of Clinical Oncology*. 1997; **15**(6): 2403-13.
  36. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007; **25**(15): 1960-6.
  37. Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *Bmc Cancer*. 2008; **8**: 82.
  38. Friedenson B. BRCA1 and BRCA2 pathways and the risk of cancers other than breast or ovarian. *MedGenMed*. 2005; **7**(2): 60.
  39. Lynch HT, Deters CA, Snyder CL, Lynch JF, Villeneuve P, Silberstein J, et al. BRCA1 and pancreatic cancer: pedigree findings and their causal relationships. *Cancer Genet Cytogenet*. 2005; **158**(2): 119-25.
  40. Hahn SA, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, et al. BRCA2 germline mutations in familial pancreatic carcinoma. *Journal of the National Cancer Institute*. 2003; **95**(3): 214-21.
  41. Ferrone CR, Levine DA, Tang LH, Allen PJ, Jarnagin W, Brennan MF, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. *J Clin Oncol*. 2009; **27**(3): 433-8.
  42. Couch FJ, Johnson MR, Rabe KG, Brune K, de Andrade M, Goggins M, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. 2007; **16**(2): 342-6.
  43. Jones S, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science (New York, NY)*. 2009; **324**(5924): 217.
  44. Slater EP, Langer P, Niemczyk E, Strauch K, Butler J, Habbe N, et al. PALB2 mutations in European familial pancreatic cancer families. *Clin Genet*. 2010; **78**(5): 490-4.
  45. Zhang F, Ma J, Wu J, Ye L, Cai H, Xia B, et al. PALB2 links BRCA1 and BRCA2 in the DNA-damage response. *Curr Biol*. 2009; **19**(6): 524-9.
  46. Hahn S, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, et al. BRCA2 germline mutations in familial pancreatic carcinoma. *Journal of the National Cancer Institute*. 2003; **95**(3): 214-21.
  47. Couch F, Johnson M, Rabe K, Brune K, de Andrade M, Goggins M, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. *Cancer epidemiology biomarkers & prevention*. 2007; **16**(2): 342-6.
  48. Van der Heijden M, Brody J, Dezentje D, Gallmeier E, Cunningham S, Swartz M, et al. In vivo therapeutic responses contingent on Fanconi anemia/BRCA2 status of the tumor. *Clinical cancer research*. 2005; **11**(20): 7508-15.
  49. McCabe N, Lord C, Tutt ANJ, Martin NMB, Smith GCM, Ashworth A. BRCA2-deficient CAPAN-1 cells are extremely sensitive to the inhibition of Poly (ADP-Ribose) polymerase: an issue of potency. *Cancer biology & therapy*. 2005; **4**(9): 934-6.
  50. Regine WF, Winter KW, Abrams R, Safran H, Hoffman JP, Konski A, et al. RTOG 9704 a phase III study of adjuvant pre and post chemoradiation (CRT) 5-FU vs. gemcitabine (G) for resected pancreatic adenocarcinoma.

- Journal of Clinical Oncology. 2006; **24**(18): 180s-s.
51. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2009; **27**(33): 5513-8.
  52. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol*. 2007; **25**(18): 2607-15.
  53. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, Andre T, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a GERCOR and GISCAD phase III trial. *Journal of Clinical Oncology*. 2005; **23**(15): 3509-16.
  54. Poplin E, Levy DE, Berlin J, Rothenberg M, Cella D, Mitchell E, et al. Phase III trial of gemcitabine (30-minute infusion) versus gemcitabine (fixed-dose-rate infusion [FDR]) versus gemcitabine plus oxaliplatin (GEMOX) in patients with advanced pancreatic cancer (E6201). *Journal of Clinical Oncology*. 2006; **24**(18): 180s-s.
  55. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *The New England journal of medicine*. 2011; **364**(19): 1817-25.
  56. Sandhu SK, Yap TA, de Bono JS. Poly(ADP-ribose) polymerase inhibitors in cancer treatment: A clinical perspective. *European Journal of Cancer*. 2010; **46**(1): 9-20.
  57. Kyle S, Thomas HD, Mitchell J, Curtin NJ. Exploiting the Achilles heel of cancer: the therapeutic potential of poly(ADP-ribose) polymerase inhibitors in BRCA2-defective cancer. *Br J Radiol*. 2008; **81**(Special\_Issue\_1): S6-11.
  58. McCabe N, Lord CJ, Tutt AN, Martin NM, Smith GC, Ashworth A. BRCA2-deficient CAPAN-1 cells are extremely sensitive to the inhibition of Poly (ADP-Ribose) polymerase: an issue of potency. *Cancer Biol Ther*. 2005; **4**(9): 934-6.
  59. van der Heijden MS, Brody JR, Dezentje DA, Gallmeier E, Cunningham SC, Swartz MJ, et al. In vivo therapeutic responses contingent on Fanconi anemia/BRCA2 status of the tumor. *Clin Cancer Res*. 2005; **11**(20): 7508-15.
  60. Tutt A, Robson M, Garber JE, Domchek S, Audeh MW, Weitzel JN, et al. Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer. *J Clin Oncol (Meeting Abstracts)*. 2009; **27**(18S): CRA501-.
  61. Audeh MW, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, Scott C, et al. Phase II trial of the oral PARP inhibitor olaparib (AZD2281) in BRCA-deficient advanced ovarian cancer. *J Clin Oncol (Meeting Abstracts)*. 2009; **27**(15S): 5500-.
  62. Kulke MH, Niedzwiecki D, Tempero MA, Hollis DR, Mayer RJ. A randomized phase II study of gemcitabine/cisplatin, gemcitabine fixed dose rate infusion, gemcitabine/docetaxel, or gemcitabine/firinotecan in patients with metastatic pancreatic cancer (CALGB 89904). *Journal of Clinical Oncology*. 2004; **22**(14): 316s-s.
  63. Colucci G, Labianca R, Di Costanzo F, Gebbia V, Carteni G, Massidda B, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol*. 2010; **28**(10): 1645-51.
  64. Heinemann V, Quetzsch D, Gieseler F, Gonnermann M, Schonekaes H, Rost A, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *Journal of Clinical Oncology*. 2006; **24**(24): 3946-52.
  65. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *The New England journal of medicine*. 2010; **362**(14): 1273-81.
  66. Lowery MA, Z.K S. Clinical outcomes in pancreatic adenocarcinoma (PAC) associated with a known BRCA mutation. 2011 Gastrointestinal Cancer Symposium, *J Clin Oncol* 29: 2011 (suppl 4; abstr 268)
  67. Lowery M, Shah M, Smyth E, Epstein A, Segal A, O R, et al. A 67-Year-Old Woman with BRCA 1 Mutation Associated with Pancreatic Adenocarcinoma. *J Gastrointest Cancer* 2010 Aug 14 [Epub ahead of print].
  68. Lowery MA, Kelsen DP, Stadler ZK, Yu KH, Janjigian YY, Ludwig E, et al. An emerging entity: pancreatic adenocarcinoma associated with a known BRCA mutation: clinical descriptors, treatment implications, and future directions. *Oncologist*. 2011; **16**(10): 1397-402.
  69. Ashworth A. Drug resistance caused by reversion mutation. *Cancer research*. 2008; **68**(24): 10021-3.
  70. Wagle N, Emery C, Berger MF, Davis MJ, Sawyer A, Pochanard P, et al. Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. *J Clin Oncol*. 2011; **29**(22): 3085-96.
  71. Kummar S, Kinders R, Gutierrez M, Rubinstein L, Parchment R, Phillips L, et al. Phase 0 clinical trial of the poly (ADP-ribose) polymerase inhibitor ABT-888 in patients with advanced malignancies. *Journal of clinical oncology*. 2009; **27**(16): 2705-11.
  72. Kulkarni MM. Digital Multiplexed Gene Expression Analysis Using the NanoString nCounter System. *Current Protocols in Molecular Biology*: John Wiley & Sons, Inc.; 2001.

73. Malkov V, Serikawa K, Balantac N, Watters J, Geiss G, Mashadi-Hosseini A, et al. Multiplexed measurements of gene signatures in different analytes using the Nanostring nCounter™ Assay System. BMC Research Notes. 2009; **2**(1): 80.
74. Camidge DR, Randall KR, Foster JR, Sadler CJ, Wright JA, Soames AR, et al. Plucked human hair as a tissue in which to assess pharmacodynamic end points during drug development studies. Br J Cancer. 2005; **92**(10): 1837-41.

## APPENDIX A

### Performance Status Criteria

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

## APPENDIX B

### CTEP MULTICENTER GUIDELINES

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

#### Responsibility of the Protocol Chair

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

#### Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

### Inclusion of Multicenter Guidelines in the Protocol

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

### Agent Ordering

Agent may be requested electronically to PMB. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application <https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx>. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account <https://eapps-ctep.nci.nih.gov/iam/> and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov) anytime.

## APPENDIX C

### Collection and Processing of Research Blood and Tissue Samples:

#### 1.1 Timing of blood and tissue sample collection:

Specimen	Patients	Time of collection
Archival Tumor Tissue	All patients enrolled to part I and part II including patients enrolled in the lead-in, non-randomized portion of part I.	Preferably before any protocol therapy is administered but may be collected at any time during the first 3 cycles of therapy.
Research Blood	All patients enrolled to arms A & B of Part 1 (except patients enrolled in the lead-in, non-randomized portion of Part I).	<p><b>1<sup>st</sup> sample:</b> Within 10 days before the first dose of any protocol therapy (including the day of the first dose).</p> <p><b>2<sup>nd</sup> sample:</b> To be drawn while the patient is receiving veliparib (if on Arm A) between days 3-12 of cycle #2 or #3.</p> <p><b>3<sup>rd</sup> sample:</b> At the time of off treatment assessments, or within 28 days of the last dose of study therapy.</p>
Tumor Biopsy (new procurement)	First 20 patients enrolled to arms A & B of Part 1 with disease accessible to biopsy and if it does not pose as a safety risk(except patients enrolled in the lead-in, non-randomized portion of Part I).	<p><b>1<sup>st</sup> biopsy:</b> Before initiation of therapy, obtain after patient has signed consent for the study and within 14 days prior to start of protocol therapy.</p> <p><b>2<sup>nd</sup> biopsy:</b> <u>ARM A:</u> To be obtained between days 3-12 of cycle #2 or cycle #3. <u>ARM B:</u> To be obtained anytime during cycle #2 or cycle #3.</p> <p><b>3<sup>rd</sup> biopsy:</b> At the time of disease progression <math>\pm</math>, obtain up to 28 days after the last dose of protocol therapy.</p>

#### 2.1 Collection of Research Bloods:

The following specimens to be obtained at each of 3 specified time points:

- 2 x 8-10ml BD vacutainer CPT tube with sodium citrate (black/blue top), to be processed within 2 hours of blood draw (for PBMC preparation)
- 2 x 8-10ml BD vacutainer CPT tube with sodium citrate (black/blue top), to be processed within 2 hours of blood draw (for BUFFY COAT preparation)
- 1 x 10ml BD vacutainer tube with clot activator (red top tube) to be processed within 1 hour of blood draw (for SERUM preparation)

## 2.2 Processing of Research Bloods:

### 2.2.1: Standard Operating Procedure (SOP) for Collection and Preparation of PBMC samples for PAR Immunoassay

#### 1. REQUIRED MATERIALS AND EQUIPMENT

- 1.1 Pipettors (100-1000  $\mu$ L, 20-200  $\mu$ L, 2-10  $\mu$ L, 0.5-10  $\mu$ L) and tips
- 1.2 Portable electronic pipet-aid
- 1.3 10-mL sterile serological pipettes
- 1.4 50-mL conical polypropylene tubes
- 1.5 15-mL conical polypropylene tubes
- 1.6 1.5 and 2-mL Sarstedt O-ring screw cap microcentrifuge tubes
- 1.7 Plasma-Lyte A USP, pH 7.4, (Baxter Cat#: 2B2544X)
- 1.8 Ice bucket and crushed ice
- 1.9 100% ethanol
- 1.10 Dry ice/100% ethanol bath
- 1.11 Eppendorf 5810 R centrifuge with a Swinging Bucket Rotor
- 1.12 Coulter model Z1D particle counter (hemacytometer may be used as alternative)
- 1.13 Disposable Coulter particle counter vials
- 1.14 Isoton II diluent
- 1.15 Hermle Z 233 M microcentrifuge

#### 2. OPERATING PROCEDURES

***Important:*** To preserve specimen integrity PBMCs should be processed through SOP Step 7.17 (freezing of the PBMC pellets) within 3 h of blood collection.

A Batch Record (Appendix 1) must be filled out for each venous blood draw.

##### 2.1 BLOOD COLLECTION AND PREPARATION

- 2.1.1 Ensure that the phlebotomist is using the recommended 8-mL Becton Dickinson Vacutainer CPTs to draw the blood samples. If necessary, supply the phlebotomist with the correct CPTs.
- 2.1.2 The research nurse is to notify the laboratory of scheduled PD sample collections, preferably giving at least 24-h notice.
- 2.1.3 The Research Specialist is to arrive at the blood collection site at least 5 min ahead of the scheduled time point(s) to ensure rapid transport to the laboratory after collection.
- 2.1.4 Record the actual time of blood collection.

***Important:*** Do not place sample(s) on ice.

- 2.1.5 The sample is transported at room temperature (RT) in a double container from the clinical collection site to the processing laboratory.

- 2.1.6 Once in the laboratory the blood sample is mixed by inverting the tube gently 5 to 8 times and then centrifuged in a swing bucket rotor at 1,500 x g for 30 min at 18 to 25 °C, without using the brake (**NO BRAKE**).
- 2.1.7 Place a pre-printed label onto a sterile 15-mL polypropylene tube.
- 2.1.8 After centrifugation, using a P-1000 pipetman 1-mL pipette, carefully remove two-thirds of the upper plasma layer (4 – 5 mL) and properly dispose of as biohazard waste. Do not disturb the underlying whitish material.
- 2.1.9 Change the pipette tip and carefully transfer the whitish layer that contains the PBMCs into the 15-mL polypropylene tube labeled for PBMCs. Discard the remaining liquid and Vacutainer CPT in the appropriate biohazard waste container(s).
- 2.1.10 Using a 10 mL serological pipette, slowly add ice-cold Plasma-Lyte A USP to the PBMCs in the 15-mL polypropylene tube to a total volume to 14 mL; cap, then mix by gentle inversion 5 to 8 times.
- 2.1.11 Centrifuge the PBMC sample in a swing bucket rotor at 430 x g for 10 min at 18 to 25 °C, with a low brake.
- 2.1.12 Using a sterile pipette, remove all of the supernatant without disturbing the cell pellet in the PBMC sample tube. Discard the supernatant into biohazard liquid waste.
- 2.1.13 Add 3 mL of Plasma-Lyte A USP to the PBMC 15-mL tube, resuspend the cell pellet by gently flicking the bottom of the tube with the index finger, and then gently pipet up and down at least 5 times using a 1-mL pipette.

### 3. PBMC Counting and Aliquoting

- 3.1 Immediately after resuspending the PBMC cell pellet, prepare a 1:500 dilution of the sample by transferring 20 µL of sample into a disposable Coulter particle counter vial containing 10 mL of Isoton II diluent.
- 3.2 Gently mix by pipetting up and down 3 to 5 times and set aside for a cell count.
- 3.3 Using a 10 mL serological pipette, slowly add ice-cold Plasma-Lyte A USP to the PBMCs in the 15-mL polypropylene tube to bring the total volume to 14 mL; cap, then mix by gentle inversion 5 to 8 times.
- 3.4 Centrifuge the cell suspension in a swing bucket rotor at 430 x g for 10 min at 18 to 25 °C, with a low brake.
- 3.5 During centrifugation, determine the cell count in the Isoton II sample using a Coulter Z1 particle counter and record on the Batch Record Spreadsheet. Typical Coulter cell counts should be between 100 to 2000 cells. The Coulter counter uses 100 µL for each read. To calculate the total cell count:  $\text{Cell count} \times 10 \times 500 \times 2.98 = \text{total PBMCs in 2.98 mL}$ . For example, a Coulter reading of 350 cells results in a cell concentration of  $1.75 \times 10^6$  cells/mL for a total of  $5.215 \times 10^6$  PBMCs.
- 3.6 Using the total cell count found in the remaining 2.98 mL (Step 7.5), calculate the volume required to make the PBMC concentration equal to  $3 \times 10^6$  cells/mL. From the example in Step 7.5,  $5.215 \times 10^6 \text{ cells} / 3 \times 10^6 \text{ cells/mL} = 1.74 \text{ mL}$ .
- 3.7 After centrifugation (Step 7.4), use a sterile pipette to remove all of the supernatant without disturbing the cell pellet in the PBMC sample tube. Discard the supernatant into biohazard liquid waste.

- 3.8 Add to the PBMC pellet the volume of Plasma-Lyte A USP calculated in Step 7.6 (Please don't use the 'example' volume!) to yield a cell suspension containing  $3 \times 10^6$  PBMCs/mL.
- 3.9 Resuspend the cell pellet by gently flicking the bottom of the tube with the index finger and then gently pipet up and down 5 times using a 1-mL pipette.
- 3.10 Transfer 0.5-mL aliquots ( $1.5 \times 10^6$  cells) of the PBMC suspension into 2-mL Sarstedt skirted micro tubes until the remaining volume of cell suspension is  $< 0.5$  mL.
- 3.11 Record the number of 2-mL Sarstedt tubes with 0.5 mL cell suspension that have been prepared in the Batch Record.
- 3.12 Pipette the residual volume of cell suspension remaining in the tube into a 1.5-mL Sarstedt tube, noting the actual volume. Label P for "partial" on the top of the tube with an alcohol resistant Sharpie. Record the estimated cell count ( $1\mu\text{L} = 3,000$  cells) of the single residual-volume tube in the Batch Record Spreadsheet.
- 3.13 Centrifuge the Sarstedt tubes in a microcentrifuge at  $10,000 \times g$  for 1 min at RT.
- 3.14 Remove as much supernatant as possible without disturbing the cell pellet. ***There should be no more than 20  $\mu\text{L}$  residual volume remaining on the pellet.***
- 3.15 Discard the supernatant into biohazardous liquid waste.
- 3.16 Snap-freeze the PBMC cell pellets using a dry ice/ethanol bath.
- 3.17 Store the frozen PBMC samples in 81-place freezer boxes, batched by patient, at  $-70^\circ\text{C}$  until analysis or shipping.

***\*\*CRITICAL: PBMC cell counts must be determined. PBMC cell pellets without cell counts are useless. Make sure to remove as much Plasma-Lyte as possible (leave  $<20 \mu\text{L}$ ). Pellets stored in Plasma-Lyte are also useless.***

A ***separate*** Batch Record is recorded for each venous blood draw.

**Note 1:** A pre-dose and post-dose sample from the same patient will have the same Patient ID, but different Specimen ID numbers.

**Note 2:** Record times using ***military time*** (24-h designation); e.g. specify 15:15 to indicate 3:15 PM.

Facility Collecting Specimens:

---

Patient ID:

---

Specimen ID:

---

Blood Volume:

---

Blood Draw Time Point:

---

Time of Venous Blood Draw;

---

Time PBMC processing started:

---

Time of cell counts:

---

PBMC yield (total cells calculated in SOP step 7.5)

---

Volume used to dilute cells to  $3 \times 10^6$  cells/ mL (SOP step 7.6):

---

Number of 0.5 mL aliquots:

---

Volume of “partial” aliquot:

---

Initials:

---

Date:

---

## Batch Record

Operator: \_\_\_\_\_ Date: \_\_\_\_\_

### **Lot numbers:**

CPT Vacutainer Product # and lot #: \_\_\_\_\_

Plasma Lyte A USP lot # and expiration date: \_\_\_\_\_

15 mL polypropylene tubes (circle one): #352097 #352196 #352096 or Lot #: \_\_\_\_\_

Cryovial lot #: \_\_\_\_\_

Trypan Blue lot # \_\_\_\_\_ Dilution vials \_\_\_\_\_

### **Serial numbers of equipment:**

P-100 Pipetman:

P-1000 Pipetman:

**NOTES; Record times using military time (24-hour designation), for example 16:15 to indicate 4:15 pm Create a new Batch Record for each patient that contributes CPT specimens**

Sample ID: \_\_\_\_\_

Study project ID: \_\_\_\_\_

Blood Volume \_\_\_\_\_ Time of Venous Blood Draw: \_\_\_\_\_

Time Lab Processing Begins: \_\_\_\_\_

Time of PBMC Transfer into Plasma Lyte A: \_\_\_\_\_

Time of Cell Counts in Hemacytometer: \_\_\_\_\_

Record the following data:

Total cell counts in each hemacytometer square counted: \_\_\_\_\_

Viable cell counts in each hemacytometer square counted: \_\_\_\_\_

Hemacytometer dilution factor: \_\_\_\_\_

Calculated viable cell concentration in suspension: \_\_\_\_\_

Viable cell yield remaining in the 5.98 cc cell suspension: \_\_\_\_\_

Volume used to resuspend cell pellet to  $3 \times 10^6$  viable PBMCs per mL: \_\_\_\_\_

Sample ID from page 1: \_\_\_\_\_

CHOOSE ONE of the following actions by checking the appropriate box:

- ☐ For PBMC yields of  $> 3 \times 10^6$  cells ( $>1.0$  mL of cell suspension):

Number of 2.0 mL cryovials with 1.0 mL cell suspension: \_\_\_\_\_ Location: \_\_\_\_\_

Number of PBMCs per 2.0 mL cryovial:  $3 \times 10^6$

- ☐ For PBMC yields of  $\leq 3 \times 10^6$  cells ( $\leq 1.0$  mL of cell suspension):

Number of 1.5 mL cryovials with  $<1.0$  mL cell suspension: \_\_\_\_\_

Location: \_\_\_\_\_

Volume of PBMC suspension added per 1.5 mL cryovial: \_\_\_\_\_ mL

Number of PBMCs per 1.5 mL cryovial: \_\_\_\_\_

Time cryovials placed into  $-80^\circ\text{C}$  storage: \_\_\_\_\_

Date/time sample information entered into NCTVL database: \_\_\_\_\_

Notes about this PBMC Preparation, including any deviations from the SOP:

### 2.2.2 SOP for Processing of Serum Samples

1. Filled red top vacutainer should sit upright after the blood is drawn at room temperature for a minimum of 30 to a maximum of 60 minutes to allow a clot to form.
2. Centrifuge the blood sample at the end of the clotting time (30-60 minutes) in a horizontal rotor (swing-out head) for 20 minutes at 1100-1300 g at room temperature. If the blood is not centrifuged immediately after the clotting time (30-60 minutes at room temperature), the tube should be refrigerated (4°C) for no longer than 4 hours.
3. Use pipette to transfer serum. Pipette serum into the labeled cryovials; aliquot volume is recommended to be 100-250 µl. Close the caps on the vials tightly. This process should be completed within 1 hour of centrifugation.
4. Check that aliquot vial caps are secure and that all vials are labeled.
5. Place all aliquots upright in a specimen box or rack in a -80°C or colder freezer. All specimens should remain at -80°C or colder prior to shipping. The samples should not be thawed prior to shipping.
6. Serum should be shipped on dry ice to MSK per instructions below.

### 2.2.3: SOP for Processing of Buffy Coat Samples

#### Collection of blood:

- Blood should be drawn into 2 x 8-10 mL BD vacutainer CPT tube with sodium citrate (black/blue top)
- Mix immediately by gentle inversion 8 to 10 times

#### Centrifugation steps:

- For best results, blood samples should be **centrifuged within two hours** of blood collection at room temperature (18-25°C). Store tube upright until centrifugation.
- Remix the blood samples immediately prior to centrifugation by gently inverting the tube 8 to 10 times.
- Centrifuge tube/blood samples at room temperature (18-25°C) in a horizontal rotor (swing-out head) for a **minimum of 20 minutes at 1500 to 1800 RCF** (Relative Centrifugal Force). Some specimens may require 30 minutes. Centrifugation beyond 30 minutes has little additional effect. The tube may be re-centrifuged if the mononuclear “band” or layer is not disturbed. Always check to see that the tube is in the proper centrifuge carrier/adaptor and balanced properly.

### Pipetting steps:

- Label a conical centrifuge tube.
- After centrifugation, mononuclear cells and platelets will be in a whitish layer just under the plasma layer
- Using a pipette, **aspirate approximately half of the plasma** from each tube **without disturbing the whitish cell layer**. The plasma aspirates should be clear so as not to contain any white cells.
- Using a fresh pipette, **collect the whitish cell layer** from the tube and transfer into a separate properly labeled 15 mL size conical centrifuge tube. This layer will contain the remaining plasma layer plus the PBMC layer. Collection of cells immediately following centrifugation will yield best results. The tube can be disposed of according to institutional SOP on the disposal of biohazardous waste.

You should now have a conical tube containing the whitish cell layers

### Step 1: Preparation of phosphate buffered saline (PBS). Please allow 15-20 minutes for this step (or may use commercially prepared PBS as an alternative).

- PBS is used for cell washing in step 2. NOTE: This will yield enough washing solution for use on both conical tubes containing PBMCs. The phosphate buffer should be prepared fresh for each subject and kept at room temperature. Any unused buffer should be discarded according to disposal SOPs at your facility.
- Fill the 250 mL graduated disposable beaker (provided in kit) up to the 200 mL mark with deionized/purified lab water. Place one phosphate buffered saline (PBS) tablet into the beaker. Make sure the tablet has dissolved completely and is completely mixed and in solution before proceeding with step 2.

### Step 2: Cell Washing Steps

- Using a fresh pipette, add PBS to bring the total volume to 15 mL in each of the graduated conical tubes containing the whitish cell layer (PBMCs). Cap the tubes. Mix cells by inverting the tubes 5 times.
- Centrifuge both conical tubes for 15 minutes at 300 RCF. Aspirate as much supernatant as possible from both tubes without disturbing cell pellets.
- Resuspend cell pellet in both conical tubes by gently vortexing or tapping tube with index finger.
- To each conical tube containing PBMC pellets, add PBS to bring volume to 10 mL in each tube. Cap tubes. Mix cells by inverting tubes 5 times.

- Centrifuge both conical tubes for 10 minutes at 300 RCF. Aspirate as much supernatant from both conical tubes as possible without disturbing cell pellet.
- Cap the conical tubes containing PBMC pellets, make sure tubes are tightly capped to prevent desiccation. Do not freeze tubes in a styrofoam tray because tubes may crack.
- Freeze the dry pellet (do not re-suspend the pellet in additional PBS) in an open tube rack at -80°C.
- Samples should be shipped on dry ice to MSK per instructions below.

### **3.1 Tissue Collection – new procurement**

#### **3.1.1 Instructions for Tumor Biopsy:**

- Metastatic sites (liver, lung, peritoneum) will be biopsied in preference to the primary tumor.
- Where possible, the same site of metastasis will be targeted for biopsy at pre and post treatment procedure.
- We aim to obtain 4 biopsy cores at each procedure to facilitate PAR immunoassays, genotyping studies and gene expression analysis. First priority for tissue obtained will be for genotyping and PAR immunoassay.
- Due to the potential for epinephrine to interfere with the PAR immunoassay, local anesthesia will ideally be with lidocaine only. If lidocaine with epinephrine is used, this should be noted on the specimen record.
- First core biopsy will be frozen in OCT.
- Second core biopsy will be placed in a cryovial and immediately flash frozen in liquid nitrogen.
- Third & fourth core biopsies will be processed as FFPE per institutional practice.
- Samples will be shipped to MSK as per instructions below.

#### **3.1.2 SOP for Biopsy Processing and Storage in OCT**

- Dissect non tumor/normal tissue first, followed by tumor to avoid contamination.
- Use disposable sterile blade and forceps.
- For tumor specimen trim off any visible non tumor surrounding tissue (e.g. fat tissue).
- Cut large tissue pieces into smaller fragments; tissue section for embedding in plastic cryo-mold should not exceed 1,5cm x 1,0cm x 0,4cm in size.
- Proceed with embedding specimen into plastic cryo-mold (eg Tissue Tek Cryo-mold #4557; 25mmx20mmx5mm; VWR Scientific):

- Place the tissue section in plastic cryo-mold with cutting surface (area of interest) facing down.
- Carefully cover a specimen with tissue freezing medium (Optimal Cutting Temperature; Tissue Tek O.C.T. Compound; VWR Scientific).
- Suspend a beaker with 100ml of isopentane (2 Methyl butane, Certified; Fisher Sci. Chemical) in liquid nitrogen (LN2) to be chilled.
- Once condensation develops at the bottom of the beaker, place the OCT embedded cryo-mold in the beaker and freeze quickly, until the OCT turns opaque and solid (~20 seconds).

If sufficient tissue is available, freeze additional specimen aliquots in cryogenic vial per instructions below:

### **3.1.3: SOP for Flash Frozen Tumor Biopsy:**

- Tissue section for cryogenic vial should not exceed 0,5 cm<sup>3</sup> in volume.
- Place the tissue section “naked” (no OCT to be added) inside cryogenic vial.
- Quickly immerse cryogenic vial in liquid nitrogen to snap freeze the tissue (~20 seconds).

#### **4.1: Shipping of Research Samples (for participating sites)**

Label all samples with the following information:

Protocol #12-045

MSK-assigned patient ID

Initials

Date of collection

Type of sample (X- biopsy, B-buffy coat, P- PBMC, S- serum)

Time point (Baseline, FU1 Wk 6, etc).

Study materials for sample collection, processing and shipping should be obtained by the site. Shipment of human samples must comply with appropriate regulations (such as U.S. DOT, IATA, and courier regulations). Samples should be packaged in a way to prevent and control breakage, spillage, or leakage.

Samples should be shipped by overnight courier so that the package can be tracked appropriately, and shipments must arrive Mondays through Fridays (no weekend delivery).

**Complete the requisition form and include with the sample ([Appendix H](#)). Research Biopsy Tissue (archival and new procurements), and Research Blood Samples should be sent according to the following Shipping Procedures:**

1. Send email at least 24 hours in advance to advise recipient of scheduled shipping time. In the email, include the shipment tracking number and the shipper's name, contact number, and email address. Address email to MSK staff Dr. Eileen

O'Reilly ([oreillye@mskcc.org](mailto:oreillye@mskcc.org)), Jacklynn Egger, ([eggerj@mskcc.org](mailto:eggerj@mskcc.org)), Shreya Vemuri ([vemuris@mskcc.org](mailto:vemuris@mskcc.org)).

2. Verify the patient ID, sample volume (if applies) and other information on the shipping list against the samples to be shipped for accuracy.
3. Place the sample tubes/vials for each patient in watertight biohazard specimen bags.
  - Appropriate temperatures for each sample shipment
    - Archival tissue – ambient
    - Part I tumor biopsy – frozen, dry ice
    - PBMC samples – frozen, dry ice
    - Serum samples – frozen, dry ice
    - Buffy coat samples – frozen, dry ice
  - For frozen samples: Place the specimen bags in a shipping container with sufficient dry ice to maintain the samples in frozen state for at least 24 hours.
4. Label the container as biohazard specimens
5. Ship the specimen to the below address via overnight delivering service (FedEx preferred). Recipient will reply via email to confirm when sample is received.

Center for Pancreas Cancer Research  
Memorial Sloan Kettering Cancer Center  
417 East 68<sup>th</sup> St., 8<sup>th</sup> Floor Rm. 853  
New York, NY 10065  
Tel: 646-888-3135

## APPENDIX D

### Gene List for Analysis

As of 10/19/2015 (N= 411)

Gene_Symbol	HGNC_ID	Description	Location
ABL1	76	c-abl oncogene 1, non-receptor tyrosine kinase	9q34.1
ACVR1	171	activin A receptor, type I	2q23-q24
AKT1	391	v-akt murine thymoma viral oncogene homolog 1	14q32.32-q32.33
AKT2	392	v-akt murine thymoma viral oncogene homolog 2	19q13.1-q13.2
AKT3	393	v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)	1q44
ALK	427	anaplastic lymphoma receptor tyrosine kinase	2p23
ALOX12B	430	arachidonate 12-lipoxygenase, 12R type	17p13.1
ANKRD11	21316	ankyrin repeat domain 11	16q24.3
APC	583	adenomatous polyposis coli	5q21-q22
AR	644	androgen receptor	Xq12
ARAF	646	v-raf murine sarcoma 3611 viral oncogene homolog	Xp11.3-p11.23
ARID1A	11110	AT rich interactive domain 1A (SWI-like)	1p36.1-p35
ARID1B	18040	AT rich interactive domain 1B (SWI1-like)	6q25.3
ARID2	18037	AT rich interactive domain 2 (ARID, RFX-like)	12q13.11
ARID5B	17362	AT rich interactive domain 5B (MRF1-like)	10q11.22
ASXL1	18318	additional sex combs like 1 (Drosophila)	20q11
ASXL2	23805	additional sex combs like 2 (Drosophila)	2p24.1
ATM	795	ataxia telangiectasia mutated	11q22-q23
ATR	882	ataxia telangiectasia and Rad3 related	3q22-q24
ATRX	886	alpha thalassemia/mental retardation syndrome X-linked	Xq21.1
AURKA	11393	aurora kinase A	20q13
AURKB	11390	aurora kinase B	17p13.1
AXIN1	903	axin 1	16p13.3
AXIN2	904	axin 2	17q23-q24
AXL	905	AXL receptor tyrosine kinase	19q13.1
B2M	914	beta-2-microglobulin	15q21-q22.2
BAP1	950	BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase)	3p21.31-p21.2
BARD1	952	BRCA1 associated RING domain 1	2q34-q35
BBC3	17868	BCL2 binding component 3	19q13.3-q13.4
BCL10	989	B-cell CLL/lymphoma 10	1p22
BCL2	990	B-cell CLL/lymphoma 2	18q21.3
BCL2L1	992	BCL2-like 1	20q11.21
BCL2L11	994	BCL2-like 11 (apoptosis facilitator)	2q13
BCL6	1001	B-cell CLL/lymphoma 6	3q27
BCOR	20893	BCL6 corepressor	Xp11.4
BIRC3	591	baculoviral IAP repeat-containing 3	11q22

BLM	1058	Bloom syndrome, RecQ helicase-like	15q26.1
BMPR1A	1076	bone morphogenetic protein receptor, type IA	10q22.3
BRAF	1097	v-raf murine sarcoma viral oncogene homolog B1	7q34
BRCA1	1100	breast cancer 1, early onset	17q21-q24
BRCA2	1101	breast cancer 2, early onset	13q12-q13
BRD4	13575	bromodomain containing 4	19
BRIP1	20473	BRCA1 interacting protein C-terminal helicase 1	17q22.2
BTX	1133	Bruton agammaglobulinemia tyrosine kinase	Xq21.33-q22
CALR	1455	calreticulin	19p13.3-p13.2
CARD11	16393	caspase recruitment domain family, member 11	7p22
CASP8	1509	caspase 8, apoptosis-related cysteine peptidase	2q33-q34
CBFB	1539	core-binding factor, beta subunit	16q22.1
CBL	1541	Cas-Br-M (murine) ecotropic retroviral transforming sequence	11q23.3-qter
CCND1	1582	cyclin D1	11q13
CCND2	1583	cyclin D2	12p13
CCND3	1585	cyclin D3	6p21
CCNE1	1589	cyclin E1	19q12
CD274	17635	CD274 molecule	9p24.1
CD276	19137	CD276 molecule	15q23-q24
CD79A	1698	CD79a molecule, immunoglobulin-associated alpha	19q13.2
CD79B	1699	CD79b molecule, immunoglobulin-associated beta	17q23
CDC73	16783	cell division cycle 73, Paf1/RNA polymerase II complex component, homolog (S. cerevisiae)	1q25
CDH1	1748	cadherin 1, type 1, E-cadherin (epithelial)	16q22.1
CDK12	24224	cyclin-dependent kinase 12	17q12
CDK4	1773	cyclin-dependent kinase 4	12q13
CDK6	1777	cyclin-dependent kinase 6	7q21-q22
CDK8	1779	cyclin-dependent kinase 8	13q12
CDKN1A	1784	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	6p21.1
CDKN1B	1785	cyclin-dependent kinase inhibitor 1B (p27, Kip1)	12p13.1-p12
CDKN2A	1787	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	9p21
CDKN2B	1788	cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4)	9p21
CDKN2C	1789	cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4)	1p32.3
CEBPA	1833	CCAAT/enhancer binding protein (C/EBP), alpha	19q13.1
CENPA	1851	centromere protein A	2p24-p21
CHEK1	1925	CHK1 checkpoint homolog (S. pombe)	11q24.2
CHEK2	16627	CHK2 checkpoint homolog (S. pombe)	22q12.1
CIC	14214	capicua homolog (Drosophila)	19q13.2
CREBBP	2348	CREB binding protein	16p13.3
CRKL	2363	v-crk sarcoma virus CT10 oncogene homolog (avian)-like	22q11.21
CRLF2	14281	cytokine receptor-like factor 2	Xp22.3 and Yp11.3

CSF1R	2433	colony stimulating factor 1 receptor	5q32
CSF3R	2439	colony stimulating factor 3 receptor (granulocyte)	1p35-p34.3
CTCF	13723	CCCTC-binding factor (zinc finger protein)	16q21-q22.3
CTLA4	2505	cytotoxic T-lymphocyte-associated protein 4	2q33
CTNNB1	2514	catenin (cadherin-associated protein), beta 1, 88kDa	3p21
CUL3	2553	cullin 3	2q36.2
CXCR4	2561	chemokine (C-X-C motif) receptor 4	2q21
DAXX	2681	death-domain associated protein	6p21.3
DCUN1D1	18184	DCN1, defective in cullin neddylation 1, domain containing 1 ( <i>S. cerevisiae</i> )	3q26.3
DDR2	2731	discoidin domain receptor tyrosine kinase 2	1q12-q23
DICER1	17098	dicer 1, ribonuclease type III	14q32.2
DIS3	20604	DIS3 mitotic control homolog ( <i>S. cerevisiae</i> )	13q21.32
DNAJB1	5270	DnaJ (Hsp40) homolog, subfamily B, member 1	19p13.2
DNMT1	2976	DNA (cytosine-5-)-methyltransferase 1	19p13.2
DNMT3A	2978	DNA (cytosine-5-)-methyltransferase 3 alpha	2p23
DNMT3B	2979	DNA (cytosine-5-)-methyltransferase 3 beta	20q11.2
DOT1L	24948	DOT1-like, histone H3 methyltransferase ( <i>S. cerevisiae</i> )	19p13.3
E2F3	3115	E2F transcription factor 3	6p22
EED	3188	embryonic ectoderm development	11q14.2-q22.3
EGFL7	20594	EGF-like-domain, multiple 7	9q34.3
EGFR	3236	epidermal growth factor receptor	7p12
EIF1AX	3250	eukaryotic translation initiation factor 1A, X-linked	Xp22.13
EIF4A2	3284	eukaryotic translation initiation factor 4A2	3q28
EIF4E	3287	eukaryotic translation initiation factor 4E	4q21-q25
EP300	3373	E1A binding protein p300	22q13.2
EPCAM	11529	epithelial cell adhesion molecule	2p21
EPHA3	3387	EPH receptor A3	3p11.2
EPHA5	3389	EPH receptor A5	4q13.1
EPHA7	3390	EPH receptor A7	6q16.3
EPHB1	3392	EPH receptor B1	3q21-q23
ERBB2	3430	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	17q11.2-q12
ERBB3	3431	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	12q13
ERBB4	3432	v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	2q33.3-q34
ERCC2	3434	excision repair cross-complementing rodent repair deficiency, complementation group 2	19q13.3
ERCC3	3435	excision repair cross-complementing rodent repair deficiency, complementation group 3 (xeroderma pigmentosum group B complementing)	2q21
ERCC4	3436	excision repair cross-complementing rodent repair deficiency, complementation group 4	16p13.3
ERCC5	3437	excision repair cross-complementing rodent repair deficiency, complementation group 5	13q22-q34

ERG	3446	v-ets erythroblastosis virus E26 oncogene homolog (avian)	21q22.3
ERRFI1	18185	ERBB receptor feedback inhibitor 1	1p36.23
ESR1	3467	estrogen receptor 1	6q24-q27
ETV1	3490	ets variant 1	7p22
ETV6	3495	ets variant 6	12p13
EZH2	3527	enhancer of zeste homolog 2 (Drosophila)	7q35-q36
FAM123B	26837	family with sequence similarity 123B	Xq11.1
FAM175A	25829	family with sequence similarity 175, member A	4q21.23
FAM46C	24712	family with sequence similarity 46, member C	1p12
FANCA	3582	Fanconi anemia, complementation group A	16q24.3
FANCC	3584	Fanconi anemia, complementation group C	9q22.3
FAT1	3595	FAT tumor suppressor homolog 1 (Drosophila)	4q35.2
FBXW7	16712	F-box and WD repeat domain containing 7	4q31.23
FGF19	3675	fibroblast growth factor 19	11q13.1
FGF3	3681	fibroblast growth factor 3	11q13
FGF4	3682	fibroblast growth factor 4	11q13.3
FGFR1	3688	fibroblast growth factor receptor 1	8p12
FGFR2	3689	fibroblast growth factor receptor 2	10q25.3-q26
FGFR3	3690	fibroblast growth factor receptor 3	4p16.3
FGFR4	3691	fibroblast growth factor receptor 4	5q33-qter
FH	3700	fumarate hydratase	1q42.1
FLCN	27310	folliculin	17p11.2
FLT1	3763	fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)	13q12
FLT3	3765	fms-related tyrosine kinase 3	13q12
FLT4	3767	fms-related tyrosine kinase 4	5q34-q35
FOXA1	5021	forkhead box A1	14q12-q13
FOXL2	1092	forkhead box L2	3q23
FOXO1	3819	forkhead box O1	13q14.1
FOXP1	3823	forkhead box P1	3p14.1
FUBP1	4004	far upstream element (FUSE) binding protein 1	1p31.1
FYN	4037	FYN oncogene related to SRC, FGR, YES	6q21
GATA1	4170	GATA binding protein 1 (globin transcription factor 1)	Xp11.23
GATA2	4171	GATA binding protein 2	3q21
GATA3	4172	GATA binding protein 3	10p15
GLI1	4317	GLI family zinc finger 1	12q13.2-q13.3
GNA11	4379	guanine nucleotide binding protein (G protein), alpha 11 (Gq class)	19p13.3
GNAQ	4390	guanine nucleotide binding protein (G protein), q polypeptide	9q21
GNAS	4392	GNAS complex locus	20q13.2-q13.3
GPS2	4550	G protein pathway suppressor 2	17p13.1
GREM1	2001	gremlin 1	15q13.3

GRIN2A	4585	glutamate receptor, ionotropic, N-methyl D-aspartate 2A	16p13.2
GSK3B	4617	glycogen synthase kinase 3 beta	3q13.3
H3F3A	4764	H3 histone, family 3A	1q42.12
H3F3B	4765	H3 histone, family 3B (H3.3B)	17q25.1
H3F3C	33164	H3 histone, family 3C	12p11.21
HGF	4893	hepatocyte growth factor (hepapoietin A; scatter factor)	7q21.1
HIST1H1C	4716	histone cluster 1, H1c	6p21.3
HIST1H2BD	4747	histone cluster 1, H2bd	6p22.1
HIST1H3A	4766	histone cluster 1, H3a	6p22.1
HIST1H3B	4776	histone cluster 1, H3b	6p22.1
HIST1H3C	4768	histone cluster 1, H3c	6p22.1
HIST1H3D	4767	histone cluster 1, H3d	6p22.1
HIST1H3E	4769	histone cluster 1, H3e	6p22.1
HIST1H3F	4773	histone cluster 1, H3f	6p22.1
HIST1H3G	4772	histone cluster 1, H3g	6p22.1
HIST1H3H	4775	histone cluster 1, H3h	6p22.1
HIST1H3I	4771	histone cluster 1, H3i	6p22.1
HIST1H3J	4774	histone cluster 1, H3j	6p22.1
HIST2H3C	20503	histone cluster 2, H3c	1q21.2
HIST2H3D	25311	histone cluster 2, H3d	1q21.2
HIST3H3	4778	histone cluster 3, H3	1q42.13
HLA-A	4931	major histocompatibility complex, class I, A	6p21.3
HNF1A	11621	HNF1 homeobox A	12q24.31
HOXB13	5112	homeobox B13	17q21.32
HRAS	5173	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	11p15.5
ICOSLG	17087	inducible T-cell co-stimulator ligand	21q22.3
ID3	5362	inhibitor of DNA binding 3, dominant negative helix-loop-helix protein	1p36.13-p36.12
IDH1	5382	isocitrate dehydrogenase 1 (NADP+), soluble	2q32-qter
IDH2	5383	isocitrate dehydrogenase 2 (NADP+), mitochondrial	15q21-qter
IFNGR1	5439	interferon gamma receptor 1	6q23-q24
IGF1	5464	insulin-like growth factor 1 (somatomedin C)	12q23.2
IGF1R	5465	insulin-like growth factor 1 receptor	15q26.3
IGF2	5466	insulin-like growth factor 2 (somatomedin A)	11p15.5
IKBKE	14552	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase epsilon	1q31
IKZF1	13176	IKAROS family zinc finger 1 (Ikaros)	7pter-7qter
IL10	5962	interleukin 10	1q31-q32
IL7R	6024	interleukin 7 receptor	5p13
INHA	6065	inhibin, alpha	2q33-qter
INHBA	6066	inhibin, beta A	7p15-p13
INPP4A	6074	inositol polyphosphate-4-phosphatase, type I, 107kDa	2q11.2
INPP4B	6075	inositol polyphosphate-4-phosphatase, type II, 105kDa	4q31.1

INSR	6091	insulin receptor	19p13.3-p13.2
IRF4	6119	interferon regulatory factor 4	6p25-p23
IRS1	6125	insulin receptor substrate 1	2q36
IRS2	6126	insulin receptor substrate 2	13q34
JAK1	6190	Janus kinase 1	1p32.3-p31.3
JAK2	6192	Janus kinase 2	9p24
JAK3	6193	Janus kinase 3	19p13-p12
JUN	6204	jun proto-oncogene	1p32-p31
KDM5A	9886	lysine (K)-specific demethylase 5A	12p11
KDM5C	11114	lysine (K)-specific demethylase 5C	Xp11.22-p11.21
KDM6A	12637	lysine (K)-specific demethylase 6A	Xp11.2
KDR	6307	kinase insert domain receptor (a type III receptor tyrosine kinase)	4q11-q12
KEAP1	23177	kelch-like ECH-associated protein 1	19p13.2
KIT	6342	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	4q11-q12
KLF4	6348	Kruppel-like factor 4 (gut)	9q31
KRAS	6407	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	12p12.1
LATS1	6514	LATS, large tumor suppressor, homolog 1 (Drosophila)	6q25.1
LATS2	6515	LATS, large tumor suppressor, homolog 2 (Drosophila)	13q11-q12
LMO1	6641	LIM domain only 1 (rhombotin 1)	11p15
MALT1	6819	mucosa associated lymphoid tissue lymphoma translocation gene 1	18q21
MAP2K1	6840	mitogen-activated protein kinase kinase 1	15q22.1-q22.33
MAP2K2	6842	mitogen-activated protein kinase kinase 2	19p13.3
MAP2K4	6844	mitogen-activated protein kinase kinase 4	17p11.2
MAP3K1	6848	mitogen-activated protein kinase kinase kinase 1	5q11.2
MAP3K13	6852	mitogen-activated protein kinase kinase kinase 13	3q27
MAP3K14	6853	mitogen-activated protein kinase kinase kinase 14	17q21-q22
MAPK1	6871	mitogen-activated protein kinase 1	22q11.2
MAPK3	6877	mitogen-activated protein kinase 3	16p11.2
MAX	6913	MYC associated factor X	14q23
MCL1	6943	myeloid cell leukemia sequence 1 (BCL2-related)	1q21
MDC1	21163	mediator of DNA-damage checkpoint 1	6p21.3
MDM2	6973	Mdm2 p53 binding protein homolog (mouse)	12q13-q14
MDM4	6974	Mdm4 p53 binding protein homolog (mouse)	1q32
MED12	11957	mediator complex subunit 12	Xq13
MEF2B	6995	myocyte enhancer factor 2B	19p13.11
MEN1	7010	multiple endocrine neoplasia I	11q13
MET	7029	met proto-oncogene (hepatocyte growth factor receptor)	7q31
MGA	14010	MAX gene associated	15q15
MITF	7105	microphthalmia-associated transcription factor	3p14.1-p12.3
MLH1	7127	mutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)	3p22.3

MLL	7132	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila)	11q23
MLL2	7133	myeloid/lymphoid or mixed-lineage leukemia 2	12q12-q13
MLL3	13726	myeloid/lymphoid or mixed-lineage leukemia 3	7q36
MPL	7217	myeloproliferative leukemia virus oncogene	1p34
MRE11A	7230	MRE11 meiotic recombination 11 homolog A (S. cerevisiae)	11q21
MSH2	7325	mutS homolog 2, colon cancer, nonpolyposis type 1 (E. coli)	2p21
MSH6	7329	mutS homolog 6 (E. coli)	2p16
MST1	7380	macrophage stimulating 1 (hepatocyte growth factor-like)	3p21
MST1R	7381	macrophage stimulating 1 receptor (c-met-related tyrosine kinase)	3p21
MTOR	3942	mechanistic target of rapamycin (serine/threonine kinase)	1p36
MUTYH	7527	mutY homolog (E. coli)	1p34.1
MYC	7553	v-myc myelocytomatosis viral oncogene homolog (avian)	8q24
MYCL1	7555	v-myc myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (avian)	1p34.3
MYCN	7559	v-myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian)	2p24.3
MYD88	7562	myeloid differentiation primary response gene (88)	3p22
MYOD1	7611	myogenic differentiation 1	11p15
NBN	7652	nibrin	8q21-q24
NCOA3	7670	nuclear receptor coactivator 3	20q12
NCOR1	7672	nuclear receptor corepressor 1	17p11.2
NEGR1	17302	neuronal growth regulator 1	1p31.1
NF1	7765	neurofibromin 1	17q11.2
NF2	7773	neurofibromin 2 (merlin)	22q12.2
NFE2L2	7782	nuclear factor (erythroid-derived 2)-like 2	2q31
NFKBIA	7797	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	14q13
NKX2-1	11825	NK2 homeobox 1	14q13.3
NKX3-1	7838	NK3 homeobox 1	8p21.2
NOTCH1	7881	notch 1	9q34.3
NOTCH2	7882	notch 2	1p13-p11
NOTCH3	7883	notch 3	19p13.2-p13.1
NOTCH4	7884	notch 4	6p21.3
NPM1	7910	nucleophosmin (nucleolar phosphoprotein B23, numatrin)	5q35.1
NRAS	7989	neuroblastoma RAS viral (v-ras) oncogene homolog	1p13.2
NSD1	14234	nuclear receptor binding SET domain protein 1	5q35
NTRK1	8031	neurotrophic tyrosine kinase, receptor, type 1	1q21-q22
NTRK2	8032	neurotrophic tyrosine kinase, receptor, type 2	9q22.1
NTRK3	8033	neurotrophic tyrosine kinase, receptor, type 3	15q24-q25
NUP93	28958	nucleoporin 93kDa	16q13
PAK1	8590	p21 protein (Cdc42/Rac)-activated kinase 1	11q13-q14

PAK7	15916	p21 protein (Cdc42/Rac)-activated kinase 7	20p12
PALB2	26144	partner and localizer of BRCA2	16p12.1
PARK2	8607	parkinson protein 2, E3 ubiquitin protein ligase (parkin)	6q25.2-q27
PARP1	270	poly (ADP-ribose) polymerase 1	1q41-q42
PAX5	8619	paired box 5	9p13.2
PBRM1	30064	polybromo 1	3p21
PDCD1	8760	programmed cell death 1	2q37.3
PDGFRA	8803	platelet-derived growth factor receptor, alpha polypeptide	4q12
PDGFRB	8804	platelet-derived growth factor receptor, beta polypeptide	5q33.1
PDPK1	8816	3-phosphoinositide dependent protein kinase-1	16p13.3
PGR	8910	progesterone receptor	11q22-q23
PHOX2B	9143	paired-like homeobox 2b	4p13
PIK3C2G	8973	phosphoinositide-3-kinase, class 2, gamma polypeptide	12p12
PIK3C3	8974	phosphoinositide-3-kinase, class 3	18q12.3
PIK3CA	8975	phosphoinositide-3-kinase, catalytic, alpha polypeptide	3q26.3
PIK3CB	8976	phosphoinositide-3-kinase, catalytic, beta polypeptide	3q21-qter
PIK3CD	8977	phosphoinositide-3-kinase, catalytic, delta polypeptide	1p36.2
PIK3CG	8978	phosphoinositide-3-kinase, catalytic, gamma polypeptide	7q22
PIK3R1	8979	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	5q13.1
PIK3R2	8980	phosphoinositide-3-kinase, regulatory subunit 2 (beta)	19q13.2-q13.4
PIK3R3	8981	phosphoinositide-3-kinase, regulatory subunit 3 (gamma)	1p34.1
PIM1	8986	pim-1 oncogene	6p21
PLCG2	9066	phospholipase C, gamma 2 (phosphatidylinositol-specific)	16q24.1
PLK2	19699	polo-like kinase 2	5q12.1-q13.2
PMAIP1	9108	phorbol-12-myristate-13-acetate-induced protein 1	18q21.32
PMS1	9121	PMS1 postmeiotic segregation increased 1 (S. cerevisiae)	2q31-q33
PMS2	9122	PMS2 postmeiotic segregation increased 2 (S. cerevisiae)	7p22.1
PNRC1	17278	proline-rich nuclear receptor coactivator 1	6q16.1
POLD1	9175	polymerase (DNA directed), delta 1, catalytic subunit 125kDa	19q13.3
POLE	9177	polymerase (DNA directed), epsilon	12q24.3
PPM1D	9277	protein phosphatase, Mg <sup>2+</sup> /Mn <sup>2+</sup> dependent, 1D	17q23.3
PPP2R1A	9302	protein phosphatase 2, regulatory subunit A, alpha	19q13
PPP6C	9323	protein phosphatase 6, catalytic subunit	9q33.3
PRDM1	9346	PR domain containing 1, with ZNF domain	6q21
PRKAR1A	9388	protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)	17q23-q24
PTCH1	9585	patched 1	9q22.1-q31
PTEN	9588	phosphatase and tensin homolog	10q23
PTPN11	9644	protein tyrosine phosphatase, non-receptor type 11	12q24.1
PTPRD	9668	protein tyrosine phosphatase, receptor type, D	9p24.1-p23
PTPRS	9681	protein tyrosine phosphatase, receptor type, S	19p13.3
PTPRT	9682	protein tyrosine phosphatase, receptor type, T	20q12-q13

RAB35	9774	RAB35, member RAS oncogene family	12q24
RAC1	9801	ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)	7p22
RAD21	9811	RAD21 homolog (S. pombe)	8q24
RAD50	9816	RAD50 homolog (S. cerevisiae)	5q23-q31
RAD51	9817	RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)	15q15.1
RAD51B	9822	RAD51-like 1 (S. cerevisiae)	14q23-q24.2
RAD51C	9820	RAD51 homolog C (S. cerevisiae)	17q25.1
RAD51D	9823	RAD51-like 3 (S. cerevisiae)	17q11
RAD52	9824	RAD52 homolog (S. cerevisiae)	12p13-p12.2
RAD54L	9826	RAD54-like (S. cerevisiae)	1p32
RAF1	9829	v-raf-1 murine leukemia viral oncogene homolog 1	3p25
RARA	9864	retinoic acid receptor, alpha	17q21.1
RASA1	9871	RAS p21 protein activator (GTPase activating protein) 1	5q13
RB1	9884	retinoblastoma 1	13q14.2
RBM10	9896	RNA binding motif protein 10	Xp11.3
RECQL4	9949	RecQ protein-like 4	8q24.3
REL	9954	v-rel reticuloendotheliosis viral oncogene homolog (avian)	2p13-p12
RET	9967	ret proto-oncogene	10q11.2
RFWD2	17440	ring finger and WD repeat domain 2	1q25.1-q25.2
RHEB	10011	Ras homolog enriched in brain	7q36
RHOA	667	ras homolog gene family, member A	3p21.3
RICTOR	28611	RPTOR independent companion of MTOR, complex 2	5p13.1
RIT1	10023	Ras-like without CAAX 1	1q21.2
RNF43	18505	ring finger protein 43	17q23.2
ROS1	10261	c-ros oncogene 1 , receptor tyrosine kinase	6q21-q22
RPS6KA4	10433	ribosomal protein S6 kinase, 90kDa, polypeptide 4	11q11-q13
RPS6KB2	10437	ribosomal protein S6 kinase, 70kDa, polypeptide 2	11q13.1
RPTOR	30287	regulatory associated protein of MTOR, complex 1	17q25.3
RUNX1	10471	runt-related transcription factor 1	21q22.3
RYBP	10480	RING1 and YY1 binding protein	3p14.2
SDHA	10680	succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	5p15
SDHAF2	26034	succinate dehydrogenase complex assembly factor 2	11q12.2
SDHB	10681	succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	1p36.1-p35
SDHC	10682	succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa	1q21
SDHD	10683	succinate dehydrogenase complex, subunit D, integral membrane protein	11q23
SETD2	18420	SET domain containing 2	3p21.31
SF3B1	10768	splicing factor 3b, subunit 1, 155kDa	2q33.1
SH2B3	29605	SH2B adaptor protein 3	12q24.12
SH2D1A	10820	SH2 domain containing 1A	Xq25

SHQ1	25543	SHQ1 homolog ( <i>S. cerevisiae</i> )	3p13
SMAD2	6768	SMAD family member 2	18q21
SMAD3	6769	SMAD family member 3	15q21-q22
SMAD4	6770	SMAD family member 4	18q21.1
SMARCA4	11100	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4	19p13.3
SMARCB1	11103	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	22q11.23
SMARCD1	11106	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1	12q13-q14
SMO	11119	smoothened homolog ( <i>Drosophila</i> )	7q32.1
SOCS1	19383	suppressor of cytokine signaling 1	16p13.13
SOX17	18122	SRY (sex determining region Y)-box 17	8q11.23
SOX2	11195	SRY (sex determining region Y)-box 2	3q26.3-q27
SOX9	11204	SRY (sex determining region Y)-box 9	17q23
SPEN	17575	spen homolog, transcriptional regulator ( <i>Drosophila</i> )	1p36
SPOP	11254	speckle-type POZ protein	17q21.33
SRC	11283	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)	20q12-q13
SRSF2	10783	serine/arginine-rich splicing factor 2	17q25.2
STAG2	11355	stromal antigen 2	Xq25
STAT3	11364	signal transducer and activator of transcription 3 (acute-phase response factor)	17q21
STAT5A	11366	signal transducer and activator of transcription 5A	17q11.2
STAT5B	11367	signal transducer and activator of transcription 5B	17q11.2
STK11	11389	serine/threonine kinase 11	19p13.3
STK40	21373	serine/threonine kinase 40	1p34.3
SUFU	16466	suppressor of fused homolog ( <i>Drosophila</i> )	10q24.32
SUZ12	17101	suppressor of zeste 12 homolog ( <i>Drosophila</i> )	17q21
SYK	11491	spleen tyrosine kinase	9q22
TBX3	11602	T-box 3	12q24.1
TCEB1	11617	transcription elongation factor B (SIII), polypeptide 1 (15kDa, elongin C)	8q13.3
TCF3	11633	transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47)	19p13.3
TCF7L2	11641	transcription factor 7-like 2 (T-cell specific, HMG-box)	10q25.3
TERT	11730	telomerase reverse transcriptase	5p15.33
TET1	29484	tet oncogene 1	10q21
TET2	25941	tet oncogene family member 2	4q24
TGFBR1	11772	transforming growth factor, beta receptor 1	9q22
TGFBR2	11773	transforming growth factor, beta receptor II (70/80kDa)	3p22
TMEM127	26038	transmembrane protein 127	2q11.2
TMPRSS2	11876	transmembrane protease, serine 2	21q22.3
TNFAIP3	11896	tumor necrosis factor, alpha-induced protein 3	6q23-q25
TNFRSF14	11912	tumor necrosis factor receptor superfamily, member 14 (herpesvirus entry mediator)	1p36.32

TOP1	11986	topoisomerase (DNA) I	20q12-q13.1
TP53	11998	tumor protein p53	17p13.1
TP63	15979	tumor protein p63	3q27-q29
TRAF2	12032	TNF receptor-associated factor 2	9q34
TRAF7	20456	TNF receptor-associated factor 7	16p13.3
TSC1	12362	tuberous sclerosis 1	9q34
TSC2	12363	tuberous sclerosis 2	16p13.3
TSHR	12373	thyroid stimulating hormone receptor	14q24-q31
U2AF1	12453	U2 small nuclear RNA auxiliary factor 1	21q22.3
VEGFA	12680	vascular endothelial growth factor A	6p12
VHL	12687	von Hippel-Lindau tumor suppressor	3p25.3
VTCN1	28873	V-set domain containing T cell activation inhibitor 1	1p12
WT1	12796	Wilms tumor 1	11p13
XIAP	592	X-linked inhibitor of apoptosis	Xq25
XPO1	12825	exportin 1 (CRM1 homolog, yeast)	2p15
XRCC2	12829	X-ray repair complementing defective repair in Chinese hamster cells 2	7q36
YAP1	16262	Yes-associated protein 1	11q13
YES1	12841	v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1	18p11.31-p11.21
ZFHX3	777	zinc finger homeobox 3	16q22.3
ZRSR2	23019	zinc finger (CCCH type), RNA-binding motif and serine/arginine rich 2	Xp22.1

MSK IRB PROTOCOL # \_\_\_\_ - \_\_\_\_

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SAE INFORMATION (CTCAE v 5.0)

SAE Start Date mm/dd/yyyy	Event	Grade <sup>1</sup>	SAE End Date mm/dd/yyyy	Relationship <sup>2</sup>	Expected <sup>3</sup>	Severity <sup>4</sup>	Intervention <sup>5</sup>

<sup>1</sup> Grades per CTCAE v5.0 = 1- Mild, 2-Moderate, 3-Severe, 4-Life Threatening or Disabling, 5-Death

<sup>2</sup> Relationship = 1-Unrelated, 2-Unlikely, 3-Possible, 4-Probable, 5-Definite

<sup>3</sup> Expected= Y-Yes, N-No

<sup>4</sup> Severity= 1-Life Threatening, 2-Disabling, 3-Hospitalized, 4-Congenital Anomaly, 5-Secondary Cancer, 6-Overdose, 7-Serious (other), 8-Not Serious

<sup>5</sup> Intervention= 1-None, 2-Interrupted, 3-Reduced, 4-Discontinued, 5-Med Given, 6-Not Applicable, 7-Surgery, 8-Hospitalized, 9-Unknown, 10-Other, 11-Transfusion, 12-Dose Not Escalated, 13-Pain Meds Lowered, 14-Interrupted/Meds Given, 15-Interrupted/Reduced

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SAE HEMATOLOGIC INFORMATION (form continues next page)

Lab Test	Lab Date mm/dd/yyyy	Lab Value	Baseline Value	Baseline Date mm/dd/yyyy	Recovery Value	Recovery Date mm/dd/yyyy

NON HEMATOLOGIC/UNEXPECTED REACTION DETAIL

Brief description of event, including relevant findings: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Complications and sequelae (including death):** \_\_\_\_\_

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**Patient's past medical history related to this event:** \_\_\_\_\_

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Reporting Information

**SAE Reported By:** \_\_\_\_\_

**Participating Site PI Name (print):** \_\_\_\_\_

**Participating Site PI Signature:** \_\_\_\_\_

**Date:** \_\_\_\_/\_\_\_\_/\_\_\_\_  
          m  m  d  d  y  y  y  y

## **APPENDIX F**

**Pill Diary: Arm A Dose Levels 2 (veliparib in combination with cisplatin/gemcitabine)**

**Pill Diary: Arm A Dose Levels 2A (veliparib in combination with cisplatin/gemcitabine)**

**Pill Diary: Arm C (veliparib single-agent)**

### Pill Diary for Arm A: Dose Levels 2

NAME: \_\_\_\_\_

MRN: \_\_\_\_\_

Number of Pills Given: \_\_\_\_\_

Pill Bottle(s) returned: **Yes** or **No**

Total Daily Dose: \_\_\_\_\_

(To be Completed by MD,RN)

**PLEASE FILL OUT AND BRING THIS SHEET TO YOUR NEXT VISIT.**

**SPECIAL INSTRUCTIONS:** *Please take AM and PM doses approximately 12 hours apart with a glass of water. Please take the medication at set times each day. Do not make up missed doses (greater than 2 hours from scheduled time).*

CYCLE #: \_\_\_\_\_ WEEKS #: \_\_\_\_\_

DAY	MEDICATION	DATE	TIME		NUMBER of 40 mg tablets taken
<b>Example</b>	VELIPARIB	<b>01/01/2012</b>	<b>9:00</b>	<b>AM</b>	<b>2</b>
	VELIPARIB		<b>9:00</b>	<b>PM</b>	<b>2</b>
<b>Day 1</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 2</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 3</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 4</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 5</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 6</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 7</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 8</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 9</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 10</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 11</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 12</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	

Patient Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Consenting Professional/RN Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Consenting Professional/RN Comments: \_\_\_\_\_

\_\_\_\_\_

**Pill Diary for Arm A: Dose Level 2A (Page 1 of 2)**

NAME: \_\_\_\_\_

MRN: \_\_\_\_\_

Number of Pills Given: \_\_\_\_\_

Pill Bottle(s) returned: **Yes or No**

Total Daily Dose: \_\_\_\_\_

(To be Completed by MD,RN)

**PLEASE FILL OUT AND BRING THIS SHEET TO YOUR NEXT VISIT.**

**SPECIAL INSTRUCTIONS:** *Please take AM and PM doses approximately 12 hours apart with a glass of water. Please take the medication at set times each day. Do not make up missed doses (greater than 2 hours from scheduled time).*

**CYCLE #:** \_\_\_\_\_ **WEEKS #:** \_\_\_\_\_

DAY	MEDICATION	DATE	TIME		NUMBER of 40 mg tablets taken
<b>Example</b>	VELIPARIB	<b>01/01/2012</b>	<b>9:00</b>	<b>AM</b>	<b>2</b>
	VELIPARIB		<b>9:00</b>	<b>PM</b>	<b>2</b>
<b>Day 1</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 2</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 3</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 4</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 5</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 6</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 7</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 8</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 9</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 10</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 11</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 12</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 13</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 14</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	

**Pill Diary for Arm A: Dose Level 2A (Page 2 of 2)**

NAME: \_\_\_\_\_

MRN: \_\_\_\_\_

**PLEASE FILL OUT AND BRING THIS SHEET TO YOUR NEXT VISIT.**

**SPECIAL INSTRUCTIONS:** *Please take AM and PM doses approximately 12 hours apart with a glass of water. Please take the medication at set times each day. Do not make up missed doses (greater than 2 hours from scheduled time).*

**CYCLE #:**

**WEEKS #:**

DAY	MEDICATION	DATE	TIME		NUMBER of 40 mg tablets taken
<b>Day 15</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 16</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 17</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 18</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 19</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 20</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 21</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	

**Patient Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Consenting Professional/RN Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Consenting Professional/RN Comments:** \_\_\_\_\_  
 \_\_\_\_\_

### Pill Diary for Arm C (Page 1 of 2)

NAME: \_\_\_\_\_

MRN: \_\_\_\_\_

Number of Pills Given: \_\_\_\_\_

Pill Bottle(s) returned: **Yes or No**

Total Daily Dose: \_\_\_\_\_

(To be Completed by MD,RN)

**PLEASE FILL OUT AND BRING THIS SHEET TO YOUR NEXT VISIT.**

**SPECIAL INSTRUCTIONS:** *Please take AM and PM doses approximately 12 hours apart with a glass of water. Please take the medication at set times each day. Do not make up missed doses (greater than 2 hours from scheduled time).*

CYCLE #: \_\_\_\_\_ WEEKS #: \_\_\_\_\_

DAY	MEDICATION	DATE	TIME		NUMBER of 100 mg tablets taken
<b>Example</b>	VELIPARIB	<b>04/01/2012</b>	<b>9:00</b>	<b>AM</b>	<b>4</b>
	VELIPARIB		<b>9:00</b>	<b>PM</b>	<b>4</b>
<b>Day 1</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 2</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 3</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 4</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 5</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 6</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 7</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 8</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 9</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 10</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 11</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 12</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 13</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	
<b>Day 14</b>	VELIPARIB			<b>AM</b>	
	VELIPARIB			<b>PM</b>	

**Pill Diary for Arm C IRB #12-045 Page 2 of 2**

NAME: \_\_\_\_\_

MRN: \_\_\_\_\_

**PLEASE FILL OUT AND BRING THIS SHEET TO YOUR NEXT VISIT.**

**SPECIAL INSTRUCTIONS:** *Please take AM and PM doses approximately 12 hours apart with a glass of water. Please take the medication at set times each day. Do not make up missed doses (greater than 2 hours from scheduled time).*

**CYCLE #:** \_\_\_\_\_ **WEEKS #:** \_\_\_\_\_

DAY	MEDICATION	DATE	TIME		NUMBER of 100 mg tablets taken
Day 15	VELIPARIB			AM	
	VELIPARIB			PM	
Day 16	VELIPARIB			AM	
	VELIPARIB			PM	
Day 17	VELIPARIB			AM	
	VELIPARIB			PM	
Day 18	VELIPARIB			AM	
	VELIPARIB			PM	
Day 19	VELIPARIB			AM	
	VELIPARIB			PM	
Day 20	VELIPARIB			AM	
	VELIPARIB			PM	
Day 21	VELIPARIB			AM	
	VELIPARIB			PM	
Day 22	VELIPARIB			AM	
	VELIPARIB			PM	
Day 23	VELIPARIB			AM	
	VELIPARIB			PM	
Day 24	VELIPARIB			AM	
	VELIPARIB			PM	
Day 25	VELIPARIB			AM	
	VELIPARIB			PM	
Day 26	VELIPARIB			AM	
	VELIPARIB			PM	
Day 27	VELIPARIB			AM	
	VELIPARIB			PM	
Day 28	VELIPARIB			AM	
	VELIPARIB			PM	

**Patient Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Consenting Professional/RN Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Consenting Professional/RN Comments:** \_\_\_\_\_

\_\_\_\_\_

## **APPENDIX G (MSK Only)**

**Laboratory Requisition: IMF/LCII MSK Research Laboratory Sample Requisition**

**Laboratory Requisition: MSK 53<sup>rd</sup> Street Research Sample Requisition**

## IMMUNE MONITORING FACILITY RESEARCH SAMPLE REQUISITION FORM

**Protocol 12-045:** A Randomized Phase II Study of Gemcitabine, Cisplatin +/- Veliparib in Patients with Pancreas Adenocarcinoma and a Known BRCA/ PALB2 Mutation (Part I) and a Phase II Single Arm Study of Single-Agent Veliparib in Previously Treated Pancreas Adenocarcinoma (Part II) (NCI #8993)

Patient Name: MRN #: DOB: Clinic Visit Date:	Send all samples to: Dr. Phillip Wong Immune Monitoring Core Facility, <b>Z-1513</b> <b>Attn:</b> Rosemarie Ramsawak, Luisa Caro, or Kevin Crawford ext. 125-3106, 125-2114
---	--

PI: Dr. Eileen O'Reilly      Research Contact Info: \_\_\_\_\_

Clinical Site Location: \_\_\_\_\_ Site Contact (Name/Email) \_\_\_\_\_

### Sample Collection Information

DRAWN BY: \_\_\_\_\_ ext. \_\_\_\_\_  
Please Print Name

DATE: \_\_\_\_\_ TIME: \_\_\_\_\_

### Requisition visit time point must be checked for samples to be processed

- ☐ **Baseline:** 2 x CPT tube  
☐ **Follow up 1:** 2 x CPT tube  
☐ **End of treatment:** 2 x CPT tube

### Research Sample Collection Instructions:

1. Invert all tubes several times immediately after collection to ensure mixing with anticoagulant (or clotting activators for serum collection tubes). For serum tubes, allow blood in tube to clot for 30 min at room temperature in a vertical position in a tube rack.
2. Adhesive labels identifying patient ID, MRN, and date of collection **must be attached** to each tube.
3. Fill in clinical date and time of collection on requisition form.
4. Place all collected tubes and all relevant sponsor kit components (vials, labels, requisition forms) in a biohazard ziplock bag at room temperature with protective padding.
5. Send specimens to Immune Monitoring Core located at the MSKCC Zuckerman Research Center (417 E. 68<sup>th</sup> St, New York, NY), **Room 1513**. Place into blood bin on benchtop.

6. Notify IMF contacts above of sample delivery. **At least 24h advanced notification should be provided using the Outlook shared blood delivery calendar: zzCAL LAB Clinical\_Trials/Shared Calendar, and be sure to include clinical site location on calendar notice.**

**Please deliver samples immediately after collection and before 5pm M-F; otherwise late processing fees will be applied or samples may be processed next day. Samples with shattered glass tubes in biohazard bag will not be processed.**

A Randomized Phase II Study of Gemcitabine, Cisplatin +/- Veliparib in Patients with Pancreas Adenocarcinoma and a Known BRCA/ PALB2 Mutation (Part I) and a Phase II Single Arm Study of Single-Agent Veliparib in Previously Treated Pancreas Adenocarcinoma (Part II) (NCI #8993)

12-045

**Memorial Sloan Kettering Cancer Center  
Research Laboratory Requisition**

PI: Eileen O'Reilly, MD

Research staff:

Name:

MRN:

DOB:

Clinic Visit Date:

Please Draw:

- 2 x 8ml Blue/Black Top Sodium Citrate CPT
- 1 x 10ml Red top

DRAWN BY: EXT: DATE: TIME

**\*\*Please contact Research staff at x0118 or x0145 when bloods are ready for pick-up\*\***

INSTRUCTIONS FOR DTU:

1. Serum and Buffy Coat processing: see protocol Appendix C
2. Appendix C enclosed with lab req
3. Please call Research staff for questions (ext. 0118)

## **APPENDIX H (Participating Site Requisitions)**

**Laboratory Requisition: Archived Tumor Tissue Shipment Form**

**Laboratory Requisition: Part I Tumor Biopsy Tissue Shipment Form**

**Laboratory Requisition: PBMC Buffy Coat and Serum Sample Shipment Form**

### Archived Tumor Tissue Shipment Form

#### Shipping Instructions:

Complete the below requisition and include with sample. Label all samples with Protocol #12-045, MSK-Assigned Participant ID, Initials, Date of Collection, and Time Point. All samples are to be prepared as per protocol [Appendix C](#). See [section 4.1](#) for labeling and shipment instructions. Notify laboratory of each shipment.

#### Participant Information

Initials:

MSK-Assigned Participant ID:

Institution:

#### Archived Tissue (All Patients) - Sample Information

Date of Biopsy/Surgery            /       /            

Accession #

Organ Site

Primary vs Metastatic      ☐ Primary Disease Site      ☐ Metastatic Site  
(Check One)

Tissue Provided      ☐ Paraffin block(s) → Provide Quantity #  
                                 ☐ Unstained slides → Provide Quantity #  
                                 ☐ Other, please specify: \_\_\_\_\_ → Provide Quantity # \_\_\_\_\_

Pathology Report Included with Submission?: ☐ YES

#### Shipment Information

##### Shipper's Contact Information

Shipment Date: \_\_\_\_\_

Shipping Courier: \_\_\_\_\_

Tracking Number: \_\_\_\_\_

##### Sender's Contact Information

Name: \_\_\_\_\_

Email: \_\_\_\_\_

Telephone Number: \_\_\_\_\_

Address: \_\_\_\_\_

##### Send shipments to:

Jacklynn Egger  
Memorial Sloan-Kettering Cancer Center  
Zuckerman Research Center  
417 East 68<sup>th</sup> St., 8<sup>th</sup> Floor Rm. 853  
New York, NY 10065

##### Confirmation of Sample Receipt (MSK ONLY):

Date Received: \_\_ / \_\_ / \_\_\_\_

Storage Location: \_\_\_\_\_

**Part I Tumor Biopsy Tissue Shipment Form**

**Shipping Instructions:**

Complete the below requisition and include with sample. Label all samples with Protocol #12-045, MSK-Assigned Participant ID, Initials, Date of Collection, and Time Point. All samples are to be prepared as per protocol [Appendix C](#). See [Section 4.1](#) for labeling and shipment instructions. Notify laboratory of each shipment.

**Participant Information**

Initials:

MSK-Assigned Participant ID:

Institution:

**Part I Tumor Biopsies (New Procurement) - Sample Information**

Date of Biopsy/Surgery            /       /            

Accession #

Organ Site

Primary vs Metastatic      ☐ Primary Disease Site      ☐ Metastatic Site  
(Check One)

Study Time Point      ☐ Baseline  
                                 ☐ During Treatment (Cycle 2 or 3, days 3-12) → List Cycle # \_\_\_\_\_  
                                 ☐ End of Treatment

Tissue Provided      ☐ Core Frozen in OCT → Provide Quantity # \_\_\_\_\_  
                                 ☐ Core in Cryovial, Flash-Frozen → Provide Quantity # \_\_\_\_\_  
                                 ☐ Core, Formalin-Fixed Paraffin-Embedded → Provide Quantity # \_\_\_\_\_

☐ Other, please specify: \_\_\_\_\_ → Provide Quantity # \_\_\_\_\_

Pathology Report Included with Submission?: ☐ YES

**Shipment Information**

**Shipper's Contact Information**

Shipment Date: \_\_\_\_\_  
Shipping Courier: \_\_\_\_\_  
Tracking Number: \_\_\_\_\_

**Sender's Contact Information**

Name: \_\_\_\_\_  
Email: \_\_\_\_\_  
Telephone Number: \_\_\_\_\_  
Address: \_\_\_\_\_

**Send shipments to:**

Jacklynn Egger  
Memorial Sloan-Kettering Cancer Center  
Zuckerman Research Center  
417 East 68<sup>th</sup> St., 8<sup>th</sup> Floor Rm. 853  
New York, NY 10065

**Confirmation of Sample Receipt (MSK ONLY):**

Date Received:      /      /

Storage Location: \_\_\_\_\_

**Research Blood: PBMCs, Buffy Coat, and Serum Sample Shipment Form**

**Shipping Instructions:**

Complete the below requisition and include with sample. Label all samples with Protocol #12-045, MSK- Assigned Participant ID, Initials, Date of Collection, and Time Point. All samples are to be prepared as per protocol [Appendix C](#). See [section 4.1](#) for labeling and shipment instructions. Notify laboratory of each shipment.

**Participant Information**

Initials:

MSK-Assigned Participant ID:

Institution:

Study Time Point:

☐ Baseline

☐ During Treatment (Cycle 2 or 3, days 3-12) → List Cycle # \_\_\_\_\_

☐ End of Treatment

**Sample Information**

Buffy Coat Sample

Date of Collection:

      /       /            

Sample Type:

☐ Pellet → Provide Quantity # \_\_\_\_\_

Serum Sample

Date of Collection:

      /       /            

Sample Type:

☐ Aliquot → Provide Quantity # \_\_\_\_\_

PBMC Sample

Date of Collection:

      /       /            

Sample Type:

☐ Aliquot → Provide Quantity # \_\_\_\_\_

**Shipment Information**

**Shipper's Contact Information**

Shipment Date: \_\_\_\_\_

Shipping Courier: \_\_\_\_\_

Tracking Number: \_\_\_\_\_

**Sender's Contact Information**

Name: \_\_\_\_\_

Email: \_\_\_\_\_

Telephone Number: \_\_\_\_\_

Address: \_\_\_\_\_

Send shipments to:

Jacklynn Egger

Memorial Sloan-Kettering Cancer Center

Zuckerman Research Center

417 East 68th St., 8th Floor Rm. 853

New York, NY 10065

Confirmation of Sample Receipt (MSK ONLY):

Date Received: \_\_ / \_\_ / \_\_\_\_

Storage Location: \_\_\_\_\_