PARPVAX: A PHASE IB/2, OPEN LABEL STUDY OF NIRAPARIB PLUS EITHER IPILIMUMAB OR NIVOLUMAB IN PATIENTS WITH ADVANCED PANCREATIC CANCER WHOSE DISEASE HAS NOT PROGRESSED ON PLATINUM-BASED THERAPY

Principal Investigator: Kim A. Reiss Binder, MD
University of Pennsylvania, Department of Internal Medicine
Division of Hematology/Oncology
Perelman Center for Advanced Medicine
South Tower, 10th Floor, Room 107
3400 Civic Center Boulevard
Philadelphia, PA 19104
(215) 360-0735 (phone); (215) 662-4646 (fax)
Email: kim.reissbinder@pennmedicine.upenn.edu

Regulatory Sponsor: University of Pennsylvania
8046 Maloney Building
3400 Spruce Street
Philadelphia, PA 19104
(215) 349-8627 (phone)
Sponsor Representative: Emma A. Meagher, MD
emma@upenn.edu

Medical Monitor: Vivek Narayan, MD

Statistician: Rosemarie Mick, MS

Investigational Products: Niraparib
Nivolumab
Ipilimumab

UPCC Number: UPCC 35217

UPenn IRB Number: 828516

IND/ IDE Number: 136726

ClinicalTrials.gov Number: NCT03404960

Initial version v.1 28 Jul 2017

Amendments

v. 1.1 14 Aug 2017

v. 2 22 Sept 2017

v. 3 23 Nov 2017

v. 4 13 Apr 2018

v. 5 29 Sept 2020

v. 6 10 Aug 2021

v. 7 7 Oct 2021

v. 8 2 Dec 2021

Table of Contents

Table of Tables

1 STUDY SUMMARY

Title	PARPVAX: A PHASE 1B/2, OPEN LABEL STUDY OF NIRAPARIB PLUS EITHER IPILIMUMAB OR NIVOLUMAB IN PATIENTS WITH ADVANCED PANCREATIC CANCER WHOSE DISEASE HAS NOT PROGRESSED ON PLATINUM-BASED THERAPY
Short Title	Niraparib Plus Ipilimumab or Nivolumab in Patients with Advanced Pancreatic Adenocarcinoma Whose Disease Has Not Progressed on Platinum-Based Chemotherapy
UPENN IRB Number	828516
Protocol Number	UPCC 35217
Phase	Clinical Phase Ib/II
Methodology	Randomized, Two Arm, Open Label
Study Duration	3.5 years
Study Center	Abramson Cancer Center at University of Pennsylvania

Objectives

Primary:

- Determine the clinical impact of combining PARP inhibition with immune checkpoint blockade in patients with advanced PDAC and durable platinum stability.
  1. Establish the safety of this combination (phase I portion)
  2. Determine clinical efficacy as measured by PFS rate at 6 months (phase II portion)

Secondary:

- To assess the proportion of tumors in this cohort (with stability or response to platinum therapy) with homologous recombination deficits (HRD)
- To examine the relationship between HRD and progression free survival with niraparib plus either nivolumab or ipilimumab.
- To evaluate for immune activation in this population prior to and during treatment with PARP inhibition plus PD-1 or CTLA-4 antagonism
- To evaluate efficacy by assessment of objective response (RECIST v.1.1) in those with measurable disease and objective response rate (ORR).To assess duration of response (DOR)
- To evaluate overall survival (OS)

Number of Subjects

84 (42 patients per arm)

Main Inclusion and Exclusion Criteria

KEY INCLUSIONS:

1. Histologically or cytologically confirmed diagnosis of pancreatic adenocarcinoma with locally advanced or metastatic disease
2. Patients must have received treatment with platinum-based (cisplatin, oxaliplatin or carboplatin) treatment for locally advanced or metastatic pancreatic cancer and have received a minimum of 16 weeks of therapy without evidence of disease progression based on the investigator's opinion

   Note: this requires at least stable imaging and a stable or decreasing tumor marker as applicable and as determined by the investigator.

   If a patient has demonstrated a biochemical and imaging response to platinum therapy and has not progressed within 16 weeks of starting this therapy but had to discontinue platinum prior to 16 weeks for a legitimate medical reason (as determined by the investigator), the patient may still be considered for the trial
3. Patients may have previously failed non-platinum containing therapy or may never have previously progressed on treatment.

   -Discontinuation of the platinum component of the regimen for chemotherapy-related toxicity is permissible provided the patient has previously received at least 16 weeks of platinum-based therapy without evidence of disease progression ≤8 weeks after treatment with the platinum agent
4. Measurable disease is not required for study entry
5. Adequate organ function
6. ECOG performance status of 0-1

KEY EXCLUSIONS:

1. Prior treatment with a PARP inhibitor, ipilimumab, nivolumab or other cytotoxic T-lymphocyte-associated protein (CTLA-4), PD-1 or PD-L1 inhibitor.
2. Patients who have demonstrated resistance to platinum agents (e.g. oxaliplatin, cisplatin) are not eligible to participate in this study
3. Clinical evidence of uncontrolled malabsorption and/or any other gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with the absorption of niraparib.

4. Received any systemic treatment for pancreatic cancer during the 14 days prior to first dose of treatment
5. Acute infection requiring intravenous antibiotics, antiviral or antifungal agents during the 14 days prior to first dose of study therapy.
6. Patients will be excluded if they have an active, known or suspected autoimmune disease, defined as: patients with a history of inflammatory bowel disease are excluded from this study, as are patients with a history of symptomatic autoimmune disease (e.g. rheumatoid arthritis, systemic progressive sclerosis (scleroderma), systemic lupus erythematosus, autoimmune vasculitis e.g. Wegener's Granulomatosis); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome).

   NOTE: Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.
7. Has a history of interstitial lung disease or active, non-infectious pneumonitis
8. Has received a live vaccine within 4 weeks prior to the first dose of trial therapy (Note: seasonal influenza vaccines for injection are generally inactivated and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist) are live attenuated vaccines and are not allowed).

Statistical Methodology

We will enroll 84 patients in a two-arm phase II design. Progression-free survival rate at 6 months (PFS6) from the start of study therapy will be the primary clinical outcome in each arm. A one sample test of the null hypothesis of a PFS6 rate equal to 44% versus the alternative hypothesis of a PFS6 rate equal to 60% will be conducted. Per each arm: with 42 patients enrolled over 36 months and with 6 months of additional follow-up, there is 81% power for the test assuming exponential survival and 5% 2-sided type I error rate.

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

2 BACKGROUND AND STUDY RATIONALE

2.1 Introduction

A subset of pancreatic cancers (PDAC) are characterized by a deficiency in DNA repair (DDR) and respond exceptionally well to platinum agents and PARP inhibitors. Mutations in BRCA1, BRCA2 and PALB2 are the most well-defined causes of DDR. Mutations in ATM, CHEK2 and other DDR genes have been identified in pancreatic cancer, but their relationship to chemotherapy response is not defined. In addition, somatic alterations such as methylation may also lead to homologous recombination deficiency (HRD). Targeting platinum-stable tumors with a durable response to therapy may enrich for a DDR population. PARP inhibition should increase tumor apoptosis and may release endogenous tumor-associated neo-antigens. However, effector T-cells are actively suppressed by the PDAC microenvironment, limiting the immune response. In vivo data show that combining PARP inhibition with immune checkpoint blockade in DDR tumors can lead to a powerful T-cell mediated anti-tumor effect.

Hypothesis: Combining PARP inhibition with immune checkpoint blockade in a population enriched for DDR PDAC will unleash an immune response against large numbers of neo-antigens, creating an anti-tumor in situ vaccine.

2.2 Background and Relevant Literature

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy. In metastatic disease, even the most commonly used first-line regimens (FOLFIRINOX and gemcitabine/abraxane) are associated with a median overall survival of <1 year [1, 2]. There is, however, a subgroup of patients who respond exceptionally well to cytotoxic therapy and maintain a durable response. For such patients, there does not exist a less toxic maintenance option and they inevitably develop cumulative and eventually prohibitive toxicities such as neuropathy, myelosuppression and fatigue. There is, therefore, a great need to (1) develop tolerable maintenance strategies for appropriately selected patients by (2) identifying biomarkers that will predict response to these specific treatments.

It is well known that a meaningful subset of PDAC is characterized by a homologous recombination deficiency (HRD)[3-5]. 3-10% of these cases are caused by an inherited germ line mutation in key genes involved in the repair of damaged DNA[6]. An additional 5% may be caused by de novo germ line mutations in the same genes [4, 5, 7, 8]. Beyond this, HR genes may also be somatically mutated resulting in a genomically unstable phenotype. Finally, there is an overlap between defects in the BRCA pathway genes, the genomically unstable phenotype and a previously described BRCA-associated mutational signature [9]. Patients of all three groups appear to have a similar phenotype, with exceptional and durable responses to platinum-based chemotherapy and to PARP inhibitors[3,10], meaning that their identification has therapeutic implications.

The identification of this likely substantial and heterogeneous sub-population is a clinical challenge for several reasons. First, the use of clinical factors such as a positive family history, multiple cancers in a single host or young age of disease onset can be helpful in identifying germ line mutations, but miss somatic ones. Additionally, recent data in prostate cancer suggest that even these clinical surrogates may be inadequate to identify patients with germline mutations [11]. Second, tumor testing with next generation sequencing (NGS) panels and germ line panels

are limited to a list of known cancer drivers, but would miss any yet-identified mutations. Finally, there is a lag time of approximately 3-4 weeks for either of these methods, while patients can often not wait on the results to start therapy.

As an alternative strategy, using the clinical surrogate marker of durable platinum stability in an otherwise unselected group of PDAC patients who are stable on treatment will presumably enrich for both germline and somatically mutated tumors. Performing broad sequencing and LOH testing of blood and tumor tissue will allow the opportunity both to prove this hypothesis and to further characterize DDR tumors.

The rationale for identifying this subgroup of patients during a period of prolonged platinum stability is twofold: First, patients who have prolonged exposure to platinum suffer cumulative toxicities of cytotoxic chemotherapy and are desperately in need of alternative maintenance strategies. Second, platinum sensitivity, at least in part, coincides with PARP inhibitor sensitivity, meaning that sensitivity to platinum agents confers sensitivity to PARP inhibitors. Likewise, resistance to platinum agents confers a resistance to PARP inhibitors [12]. Therefore, waiting for these tumors to become platinum resistant prior to initiating PARP inhibitor-based treatment is not appropriate.

In the setting of ongoing platinum stability, the treatment of DDR tumors with PARP inhibition should increase tumor cell apoptosis, resulting in a concomitant rise in endogenous tumor-associated or –specific antigens (TAA, TSA) that may prime for a subsequent immune response. However, a major barrier to immune activation is the highly immunosuppressive PDAC microenvironment. PDAC tumors are infiltrated with regulatory T-cells (Tregs) and have a paucity of immune effector cells. The tumor, therefore, actively suppresses the adaptive immune response [13]. The addition of immune checkpoint blockade should off-set this suppression and allow for a rise in immune activity.

Preclinical *in vivo* data by Adams et al demonstrates that in an HRD model of ovarian cancer, the combination of CTLA-4 antibodies plus PARP inhibition resulted in a T-cell mediated tumor clearance. This effect led to a significant survival benefit for the animals and was dependent on a rise in local levels of IFN-gamma[14]. The clinical combination of PARP inhibition and immune checkpoint blockade in an ovarian cancer model is currently in phase II testing (NCT 02657889). In a second preclinical model, breast cancer cell lines and xenograft tumors were treated with PARP inhibition followed by an assessment of PD-L1 expression. PARP inhibition was found to up-regulate PD-L1 expression, and blockade of PD-L1 of these cells resulted in T-cell killing.

We hypothesize, therefore that combining PARP inhibition with either CTLA4 or PD1 blockade in a population of PDAC patients enriched for those with an HRD will result in a powerful anti-tumor effect by unleashing an immune response against large numbers of neo-antigens. Our mission is to further characterize and identify HRD PDAC patients and to identify a low-toxicity maintenance strategy for these people following successful induction chemotherapy.

Our specific aims are:

- Determine the clinical impact of combining PARP inhibition with immune checkpoint blockade in patients with advanced PDAC and durable platinum stability.
- Establish the safety of this combination

- Determine clinical efficacy as measured by PFS at 6 months, ORR, DOR and OS.
- Determine the immune pharmacodynamics of combining PARP inhibition with immune checkpoint blockade by analyzing the tumor microenvironment and peripheral blood for evidence of an increased immune response and reduction in immunosuppression
- Identify and further characterize deficits in DNA repair in patients with advanced PDAC and sustained platinum stability by performing broad sequencing of ctDNA and tumor tissue.

Clinical impact: It has become increasingly evident that a substantial subpopulation of PDAC is driven by germline or somatic deficits in DNA repair. These tumors classically respond exceptionally well to platinum-based therapies with durable responses to treatment. However, prolonged exposure to platinum-based chemotherapies leads to cumulative toxicities that eventually become prohibitive. The characterization of this subpopulation of patients coupled with the development of tailored, less toxic maintenance treatment strategies represents an important step forward in pancreatic cancer care.

2.3 Name and Description of the Investigational Products

2.3.1 Niraparib

Niraparib is an orally available, selective PARP1 and -2 inhibitor.

The chemical name for niraparib is 2-{4-[(3*S*)-piperidin-3-yl]phenyl}-2*H*-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1). The empirical molecular formula for niraparib is $C_{26}H_{30}N_4O_5S$ and its molecular weight is 510.61.

Niraparib tosylate monohydrate drug substance is a white to off-white, non-hygroscopic crystalline solid. Niraparib solubility is pH independent below the pKa of 9.95, with an aqueous free base solubility of 0.7 mg/mL to 1.1 mg/mL across the physiological pH range.

Niraparib is supplied in HDPE bottles with child resistant closures.

Niraparib does not contain gluten.

2.3.2 Nivolumab

Nivolumab, also referred to as BMS-936558-01 or BMS-936558, is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. The physical and chemical properties of nivolumab are provided below.

BMS Number	BMS-936558-01
Other Names	Nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1
Molecular Weight	146,221 daltons (143,619.17 daltons, protein portion)
Appearance	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present
Solution pH	5.5 to 6.5

Nivolumab Injection, 100 mg/10 mL (10 mg/mL),

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug final products is the vial fill volume.

2.3.3 Ipilimumab

Ipilimumab (BMS-734016, MDX-010) is a fully human IgG1κ consisting of 4 polypeptide chains; 2 identical heavy chains primarily consisting of 447 amino acids each with 2 identical kappa light chains consisting of 215 amino acids each linked through inter-chain disulfide bonds. The physical and chemical properties of ipilimumab drug substance are provided in the table below.

BMS Number	734016
Molecular Weight	147,991 Daltons
Appearance	Clear to slightly opalescent, colorless to pale yellow liquid, may contain particles
Solution pH	7.0
pI	The isoelectric focusing analysis generates a banding pattern in the pI range of 8.5 to 8.8, with the major isoform at an approximate pI of 8.7.

Ipilimumab injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles. Ipilimumab injection, 50 mg/10 mL and 200 mg/40 mL, is supplied in 10-cc or 50-cc Type I flint glass vials, respectively, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5 mg/mL at a pH of 7.0.

2.4 Niraparib Background and Data

2.4.1 Niraparib Pharmacology

Niraparib is a selective PARP-1 and -2 inhibitor that selectively kills tumor cells in vitro and in mouse xenograft models. PARP inhibition leads to irreparable DSBs, use of the error-prone DNA repair pathway, resultant genomic instability and ultimately cell-death. Additionally, PARP trapping at genetic lesions as a result of the suppression of auto-parlyation can contribute to cytotoxicity.

2.4.2 Niraparib Pharmacokinetics, Metabolism and Drug-Drug Interaction Potential

Absorption: Following a single-dose administration of 300 mg niraparib under fasting conditions, niraparib was measurable in plasma within 30 minutes and the mean peak plasma concentration (Cmax) for niraparib was reached in about 3 hours [804 ng/mL (%CV:50.2%)]. Following multiple oral doses of niraparib from 30 mg to 400 mg once daily, accumulation of

niraparib was approximately 2 fold. The systemic exposures (Cmax and AUC) to niraparib increased in a dose proportional manner when the dose of niraparib increased from 30 mg to 400 mg. The absolute bioavailability of niraparib is approximately 73%, indicating minimal first-pass effect. Concomitant administration of a high fat meal did not significantly affect the PK of niraparib after administration of 300 mg of niraparib.

Distribution: Niraparib was moderately protein bound to human plasma (83.0%). The apparent Vd/F was 1220 L, indicating extensive tissue distribution of niraparib. In a population PK analysis, the Vd/F of niraparib was 1074 L in cancer patients.

Metabolism: Niraparib is metabolized primarily by CEs to form a major inactive metabolite, M1. In a mass balance study, M1 and M10 (the subsequently formed M1 glucuronides) were the major circulating metabolites. The mean half-life of M1 was 88 hours. The exposure ratio of M1 to niraparib was approximately 1.3-2.2 fold in plasma.

Elimination: Following a single oral 300-mg dose of niraparib, the mean terminal half-life of niraparib ranged from 48 to 51 hours (approximately 2 days). In a population PK analysis, the apparent total clearance of niraparib was 16.2 L/h in cancer patients. Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following administration of a single oral 300 mg dose of [14C]-niraparib, on average 86.2% (range 71% to 91%) of the dose was recovered in urine and feces over 21 days. Radioactive recovery in the urine accounted for 47.5% (range 33.4% to 60.2%) and the feces for 38.8% (range 28.3% to 47.0%) of the dose. In pooled samples collected over 6 days, 36.7% of the dose was recovered in the urine primarily as metabolites and 21.1% of the dose was recovered in the feces primarily as unchanged niraparib.

Specific Populations:

Geriatric Patients: Population PK analyses indicated that age had no significant impact on the PK of niraparib.

Racial or Ethnic Groups: Population PK analyses indicated that race had no significant impact on the PK of niraparib.

2.4.3 Niraparib Toxicology

Carcinogenesis: No carcinogenicity studies have been conducted with niraparib.

Mutagenesis: Niraparib was clastogenic in an in vitro mammalian chromosomal aberration assay and in an in vivo rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of niraparib and indicates potential for genotoxicity in humans. Niraparib was not mutagenic in a bacterial reverse mutation assay (Ames) test.

Impairment of Fertility: No nonclinical reproductive studies have been conducted with niraparib, but a reversible decrease in spermatogenesis was observed in rats and dogs. It is not known whether niraparib or its metabolites are excreted in milk.

Animal Toxicology: In repeat-dose oral toxicity studies, niraparib was administered daily for up to 3 months duration in rats and dogs. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral hematology parameters. Additionally, decreased spermatogenesis was seen in both species. These findings occurred at

exposures below those seen clinically. All findings showed reversibility within 4 weeks of cessation of dosing.

Phototoxicity: Niraparib did not exhibit cutaneous or ocular phototoxicity in a 3-day repeat-dose study in pigmented rats.

2.4.4 Niraparib Clinical Studies

Kindly refer to the niraparib IB for clinical study updates.

The safety and efficacy of niraparib as maintenance therapy was studied in a Phase 3 randomized, double-blind, placebo-controlled trial (NOVA) in patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. All patients had received at least two prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-based regimen.

Eligible patients were assigned to one of 2 cohorts based on the results of a germline *BRCA* mutation test. Women who were hereditary germline *BRCA* mutation carriers were assigned to the g*BRCA*mut cohort (n = 203) and women who did not carry a hereditary germline *BRCA* mutation were assigned to the non-g*BRCA*mut cohort (n = 350). Within each cohort, patients were randomized using a 2:1 allocation of niraparib to placebo. Randomization occurred within 8 weeks of the last dose of the most recent platinum-containing regimen.

The primary endpoint, PFS, was determined by central independent assessment per RECIST (version 1.1) or clinical signs and symptoms and increased CA-125. PFS as defined in the NOVA study was measured from the time of randomization (which occurred up to 2 months after completion of the most recent chemotherapy regimen) to disease progression or death.

Prior to unblinding of the study, tumors from patients randomized to the non-g*BRCA*mut cohort were tested for the presence of HRD using the Myriad myChoice® HRD test, which evaluates three independent biomarkers of tumor genome instability: loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions. Tumors with homologous recombination deficiencies and those with somatic *BRCA* mutations were defined as HRDpos.

PFS was significantly longer for patients who received niraparib compared to those who received placebo for all three primary efficacy populations. Within the g*BRCA*mut cohort, the median PFS from time of randomization was 21.0 months with niraparib versus 5.5 months with placebo. In the overall non-g*BRCA*mut cohort, the median PFS from time of randomization was 9.3 months with niraparib versus 3.9 months with placebo. PFS was also significantly longer with niraparib than with placebo in the HRDpos group of the non-g*BRCA*mut cohort: 12.9 months versus 3.8 months.

2.4.5 Baseline Platelet Count and Weight as Predictors of Thrombocytopenia

An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase I study, PN001. This analysis determined that only baseline platelets had an impact on platelet nadir; lower baseline platelets (<180 109/L) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76%) or Grade ≥ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at

baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, Grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24%) compared to patients in the highest quartile (10%).

The potential relationship between body weight and TEAEs was further explored in an analysis to evaluate the correlation of grade 3 or 4 thrombocytopenia and baseline body weight. The lowest platelet count in the first 30 days was plotted versus baseline body weight to determine if low body weight identified a subgroup of patients with higher levels of thrombocytopenia during Cycle 1. In the first 30 days of treatment, a baseline body weight >77 kg is associated with a lower incidence of grade 3 or 4 thrombocytopenia (14%) relative to the group with body weight <58 kg (43%).

Finally, a classification tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing ≥Grade 3 thrombocytopenia within 30 days after the first dose of niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg or baseline platelet count <150,000 μL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of patients with a body weight >77 kg and a platelet count >150,000 μL. Further, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000 μL, and was only 206 mg for patients with body weight < 77 kg or platelet count <150,000 μL. Thus, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. These observations are to be confirmed in the present study with the inclusion of study treatment dosed at 200 mg (2 capsules of niraparib or placebo) in patients whose baseline weight is <77 kg or baseline platelet count is <150,000 μL.

2.5 Ipilimumab

2.5.1 Clinical Pharmacodynamics

CTLA-4 is a key regulator of T-cell activity. Ipilimumab is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of tumor reactive T-effector cells that mobilize to mount a direct T-cell immune attack against tumor cells. Preclinical data indicate that CTLA-4 blockade can also reduce Treg function, which may lead to an increase in anti-tumor immune response. Ipilimumab may selectively deplete Tregs at the tumor site, leading to an increase in the intratumoral T-effector/Treg cell ratio which drives tumor response leading to cell death.[21]

2.5.2 Pharmacokinetics

The PPK of ipilimumab was studied in 785 subjects (3200 serum concentrations) with advanced melanoma in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022), 1 Phase 3 study (CA184024), and 1 Phase 1 study (CA184078). The PPK analysis demonstrated that the PK of ipilimumab is linear, the exposures are dose proportional across the tested dose range of

0.3 to 10 mg/kg, and the model parameters are time-invariant, similar to that determined by non-compartmental analyses.

Upon repeated dosing of ipilimumab, administered q3w, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less, and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab CL of 16.8 mL/h from PPK analysis is consistent with that determined by non-compartmental PK analysis. The terminal T-HALF and Vss of ipilimumab calculated from the model were 15.4 days and 7.47 L, respectively, which are consistent with that determined by noncompartmental analysis. Volume of central compartment (Vc) and peripheral compartment were found to be 4.35 and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and, subsequently, into extracellular fluid space. CL of ipilimumab and Vc were found to increase with increase in BW. However, there was no significant increase in exposure with increase in BW when dosed on a milligram/kilogram basis, supporting dosing of ipilimumab based on a weight normalized regimen. The PK of ipilimumab is not affected by age, gender, race, and immunogenicity (anti-drug antibody [ADA] status); concomitant use of chemotherapy; prior therapy; BW; performance status; or tumor type. Other covariates had effects that were either not statistically significant or were of minimal clinical relevance.

2.5.3 Clinical Studies

Kindly refer to the ipilimumab IB for clinical study updates.

BMS and Medarex (acquired by BMS in Sep-2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing more than 19,500 subjects (total number of subjects enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, including a compassionate use. The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

Phase 3 programs are ongoing in melanoma, prostate cancer, and lung cancer. In melanoma, completed Phase 3 studies (MDX010-20 and CA184024) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma with a manageable safety profile, respectively. An ongoing Phase 3 study (CA184029) in melanoma is investigating ipilimumab as adjuvant monotherapy for high-risk Stage III melanoma. In addition, a Phase 3 study (CA184169) comparing the safety and efficacy of 3 versus 10 mg/kg ipilimumab monotherapy in pretreated or treatment-naïve subjects with unresectable or metastatic melanoma is ongoing.

The completed Phase 3 study (CA184043) evaluated ipilimumab in subjects with mCRPC who had progressed during or following treatment with docetaxel. Eligible subjects were randomized to a single dose of bone-directed RT, followed by either ipilimumab 10 mg/kg or placebo (799 randomized: 399 ipilimumab and 400 placebo). This study did not meet its primary endpoint of OS. The HR of 0.85 (95% CI: 0.72, 1.00) for survival favored ipilimumab but did not reach statistical significance with a P value of 0.053. Planned sensitivity analyses favored ipilimumab, where the greatest benefit appeared to be in subgroups defined by good prognostic features and low burden of disease. Additional evidence of ipilimumab activity observed in the study included a reduced risk of disease progression relative to placebo (HR = 0.70), superior clinical outcomes

compared to placebo in tumor regression, and declines in PSA. The safety profile in this study was consistent with the previously defined AE profile at the same dose.

A second Phase 3 study (CA184095) evaluated ipilimumab 10 mg/kg versus placebo in subjects with asymptomatic or minimally symptomatic, chemotherapy-naïve mCRPC with no visceral metastases.

Activity was also observed in a large Phase 2 study in lung cancer (NSCLC and SCLC; CA184041) in combination with chemotherapy. Two ongoing Phase 3 studies are evaluating ipilimumab in combination with chemotherapy in squamous NSCLC (CA184104) and SCLC (CA184156). In Study CA184104, the last patient, last visit was achieved in June-2015, and database lock occurred on 01-Sep-2015. No final data are currently available, but preliminary data indicate that no new safety concerns were identified in the course of standard clinical safety monitoring of the study. In Study CA184156, preliminary data indicate the primary endpoint of prolonging survival was not achieved, but no new safety signals were identified.

While the types of safety events observed in subjects receiving ipilimumab do not appear to change, even in combination with other anti-cancer agents, the proportion of subjects experiencing 1 type or another irAE may be impacted by the choice of combination partner. Skin and GI irAEs predominate in monotherapy studies. In combination with DTIC (melanoma), the incidence of skin and GI irAEs was lower than expected, and the incidence of hepatic irAEs was higher. In combination with paclitaxel and carboplatin (NSCLC), the incidence of all types of irAEs appeared to be numerically lower compared to the incidence observed for ipilimumab monotherapy in the Phase 2 program. In a Phase 1 study (CA184161), the concomitant administration of vemurafenib and ipilimumab in subjects with BRAF-mutated metastatic melanoma resulted in asymptomatic and reversible increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), exceeding the incidence to be expected when either agent is administered as a single agent therapy, leading to discontinuation of this treatment. In a Phase 2 study (CA184240), sequential treatment with vemurafenib followed by 10 mg/kg ipilimumab in subjects with BRAF-mutated metastatic melanoma was tolerable with a manageable safety profile. No significant signals of hepatobiliary toxicity were reported. The benefit/risk of this sequence needs to be evaluated further based on individual subject characteristics and new treatment options.

Ipilimumab is also being evaluated in clinical studies conducted independently by the Cancer Therapy Evaluation Program of the US NCI, as well as in several additional externally-sponsored studies.

2.6 Nivolumab

2.6.1 Nivolumab Clinical Pharmacodynamics

The clinical pharmacodynamics (PD) were assessed for nivolumab monotherapy and for nivolumab in combination with ipilimumab.

The PD effects of nivolumab were studied by assessing receptor occupancy (RO), peripheral immune cell population modulation, systemic cytokine modulation, and change in absolute lymphocyte count (ALC) in studies MDX1106-03 and/or CA209009. Results were as follows:

- Peripheral RO of PD-1 is saturated at doses ≥0.3 mg/kg dose levels as measured on CD3+ cells from frozen and fresh PBMCs.

- Nivolumab treatment had no clinically meaningful changes in activated T-cells in peripheral blood; no dose response was evident.
- Mean ALC measured over time did not change at any nivolumab dose nor was it associated with response to nivolumab.
- Baseline measurements of select immune cell subsets were not associated with response to nivolumab.
- Median percent increase from baseline to post-dose for CXCL9 and CXCL10 were consistent with demonstration of immunomodulatory activity of nivolumab on these chemokines.

To understand if the effect of nivolumab in combination with ipilimumab was distinct from that of either nivolumab or ipilimumab monotherapy, changes in immunomodulatory PD biomarkers with combination nivolumab and ipilimumab treatment was assessed in study CA209004. ALC, activated CD4+ and CD8+ T cells in the periphery, and levels of inflammatory cytokines were measured in blood and serum in CA209004. Results were as follows:

- No consistent rise in ALC was observed with combination nivolumab and ipilimumab therapy, similar to nivolumab monotherapy.
- Increases in activated CD4+ and CD8+ T cells were observed with the combination regimen, consistent with the pharmacodynamic effects of ipilimumab alone and distinct from the effects of nivolumab alone.
- Combination therapy resulted in increases in interferon-γ induced serum cytokines, such as MIG (CXCL9) and IP-10 (CXCL10), which are also increased with single agent nivolumab.

2.6.2 Nivolumab Pharmacokinetics

Single Dose Pharmacokinetics: Single-dose PK of nivolumab was studied in 39 subjects with cancer. The single-dose PK of nivolumab was linear and dose-proportional in the range of 0.3 mg/kg to 10 mg/kg. The mean terminal T-HALF of nivolumab ranged between 17 and 25 days across the dose range of 0.3 mg/kg to 10 mg/kg. Geometric mean total clearance varied from 0.13 mL/h/kg to 0.19 mL/h/kg, while mean volume of distribution varied between 83 mL/kg and 113 mL/kg across doses. The clearance and half-life of nivolumab are consistent with that of IgG4.

Multiple-dose Pharmacokinetics: The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Based on a population pharmacokinetic (PPK) analysis using data from patients with various tumor types, including melanoma, NSCLC, and RCC and a time varying CL model, nivolumab clearance was shown to decrease over time, with a median maximal reduction from baseline values of approximately 25% resulting in a geometric mean steady state clearance (CLss) (% coefficient of variation [CV%]) of 8.2 mL/h [53.9%]. The decrease in CLss is not considered to be clinically relevant. The geometric mean [CV%] volume

of distribution at steady state (Vss) is 6.8 L (27.3%), and elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1, solid tumor type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggested that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients.

2.6.3 Nivolumab Drug-Drug Interactions

Although monoclonal antibodies are not direct inhibitors/inducers of metabolizing enzymes, recent literature reports suggest that therapeutic proteins that are modulators of cytokines may indirectly affect expression of cytochrome (CYP) enzymes. The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes, at single and multiple doses of 0.3 to 10 mg/kg Q3W from CA209009.

There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2 and 10 mg/kg) during the course of treatment. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system). These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab.

2.6.4 Nivolumab Clinical Studies

Nivolumab has demonstrated clinical activity in subjects with a variety of malignancies. Kindly refer to the nivolumab IB for clinical trial updates.

Nivolumab monotherapy (OPDIVO™) was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the US and EU, and has been approved for several other indications (e.g., metastatic NSCLC, advanced RCC, cHL). Nivolumab is also approved in combination with ipilimumab (YERVOY™) for unresectable or metastatic melanoma in multiple countries, including the US and EU.

In addition to the current approvals, nivolumab is currently being tested in the following clinical studies:

NSCLC:

- CA209012: ongoing Phase 1 study with nivolumab in combination with ipilimumab, platinum-based chemotherapy or erlotinib in subjects with treatment-naive Stage IIIB/IV NSCLC
- ONO-4538-04: completed Phase 1, open-label study of nivolumab in combination with chemotherapy in Japanese subjects with Stage IIIB/IV or recurrent NSCLC.

RCC:

- CA209016: ongoing Phase 1 dose-escalation study of nivolumab in combination with VEGFR-TKIs or ipilimumab in subjects with metastatic RCC

cHL:

- ONO-4538-15: completed, Phase 2 open-label study of nivolumab in Japanese subjects with relapsed or refractory cHL

SCCHN:

- CA209141: completed Phase 3, randomized, open-label study of nivolumab vs investigator's choice therapy in recurrent or metastatic platinum-refractory SCCHN

SCLC:

- CA209032: ongoing Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors, including SCLC

Gastric Cancer:

- ONO 12: Nivolumab (ONO-4538/BMS-936558) as Salvage Treatment After Second- or Later-Line Chemotherapy for Advanced Gastric or Gastroesophageal Junction Cancer (AGC): A Double-Blinded, Randomized, Phase 3 Trial

Colorectal Cancer:

- CA209142: ongoing Phase 2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with recurrent or metastatic microsatellite instability high (MSI-H) colorectal cancer

2.7 Niraparib Plus Immune Checkpoint Blockade

Niraparib has recently been combined with pembrolizumab in the phase I/II TOPACIO study (NCT02657889). Although this study is currently recruiting participants, the phase I portion is complete and the recommended Phase 2 dose of niraparib was established as 200 mg oral niraparib once daily. The most common treatment related grade ≥ 3 adverse events occurring in ≥ 2 patients included anemia (35.7%), thrombocytopenia (35.7%), neutropenia (14.3%) and decreased platelet counts (14.3%). Data from the phase 2 is going and less than 7% of Phase 2 patients had experienced grade ≥3 thrombocytopenia during the first treatment cycle. Thirty patients (36.1%) enrolled in Phase 2 reported treatment-related grade ≥3 adverse events

including anemia (8.4%), fatigue (6.0%), platelet count decrease (6.0%) and thrombocytopenia (6.0%)[15].

The final starting dose of 200 mg has been established. The starting dose could be reduced if additional data indicates that reduction of the starting dose may be warranted.

We do not expect any overlapping toxicity between the combination of niraparib and nivolumab or niraparib and ipilimumab, given the known toxicities of these agents. Therefore, we chose full dose of checkpoint inhibition plus niraparib based on the available clinical data with PD-1. However, we have added a safety hold after 3 patients have enrolled for each arm to ensure that dose modifications do not need to be made.

3 STUDY OBJECTIVES

3.1 Primary Objective

- Determine the clinical impact of combining PARP inhibition with immune checkpoint blockade in patients with advanced PDAC and durable platinum stability.
- Establish the safety of this combination
- Determine clinical efficacy as measured by the PFS rate at 6 months

3.2 Secondary Objectives

- To assess the proportion of tumors in this cohort (with stability or response to platinum therapy) with homologous recombination deficits (HRD).
- To examine the relationship between HRD and progression free survival with niraparib plus either nivolumab or ipilimumab.
- To evaluate for immune activation in this population prior to and during treatment with PARP inhibition plus immune checkpoint blockade (PD-1 or CTLA-4 antagonism).
- To evaluate the efficacy by assessment of objective response (RECIST v.1.1) in those with measurable disease and objective response rate (ORR).
- To assess duration of response (DOR)
- To evaluate overall survival (OS)

4 INVESTIGATIONAL PLAN

4.1 General Design

This is a two arm, open-label randomized study of niraparib plus either ipilimumab or nivolumab in patients with locally advanced or metastatic pancreatic adenocarcinoma who have achieved stability on platinum-based therapy.

Patients will be randomized to either Arm A (niraparib + nivolumab) or Arm B (niraparib + ipilimumab). No more than 6 patients will be treated over a 2-week period without approval of

the Penn PI and Sponsor. During the DLT period after the third patient in each Arm is enrolled, enrollment will be suspended until the third patient has received the second dose of either nivolumab in Arm A or ipilimumab in Arm B on Cycle 2 Day 1. The first 3 weeks are considered the "DLT evaluation period".

4.1.1 Screening Phase

All patients will undergo screening assessments within 28 days prior to the first dose of therapy. AEs that occur after signing of the informed consent form and before administration of the first treatment dose will also be collected during this period.

Screening assessments will include demographics and medical history, family history, prior treatments for pancreatic cancer (and other malignancies if applicable), prior and current medications and procedures, ECOG performance status, hematology, whole blood sample for cytogenetic analysis, serum chemistry, serum pregnancy for women of childbearing potential, urinalysis, physical examination, vital signs, weight and height measurements, adverse events, and radiological assessment by CT or magnetic resonance imaging (MRI). For patients who pass the screening phase, a tumor biopsy prior to first dose of treatment will be collected from patients for whom this is deemed safe and feasible. Archival tumor tissue samples, if available, will also be collected and stored.

All patients will have blood collected prior to treatment for correlative analyses and storage.

4.1.2 Study Intervention Phase

During the treatment phase (continuous 28 day cycles (Arm A) or continuous 21 day cycles (Arm B)), patients will be monitored for safety and efficacy. Assessments during the treatment phase will include AEs, ECOG performance status, concomitant medications and procedures, physical examination, vital signs and weight measurements, hematology and serum chemistry, serum or urine pregnancy (per investigator discretion) for women of childbearing potential, CA 19-9 measurement, blood samples for research analyses and study drug administration and accountability. An on-treatment tumor biopsy will be obtained if considered safe and feasible. A biopsy is not required if there appears to be no evidence of disease (complete remission). Patients will be assessed for disease status per RECIST v1.1 after every 2nd cycle of treatment (Arm A) or every 3rd cycle of treatment (Arm B). Patients will continue to receive treatment until disease progression or other reason for treatment discontinuation.

Patients will be monitored continuously for safety.

4.1.3 Treatment Discontinuation

Upon treatment discontinuation, all patients will return to the clinic for an End of Treatment (EOT) visit if they are able to.

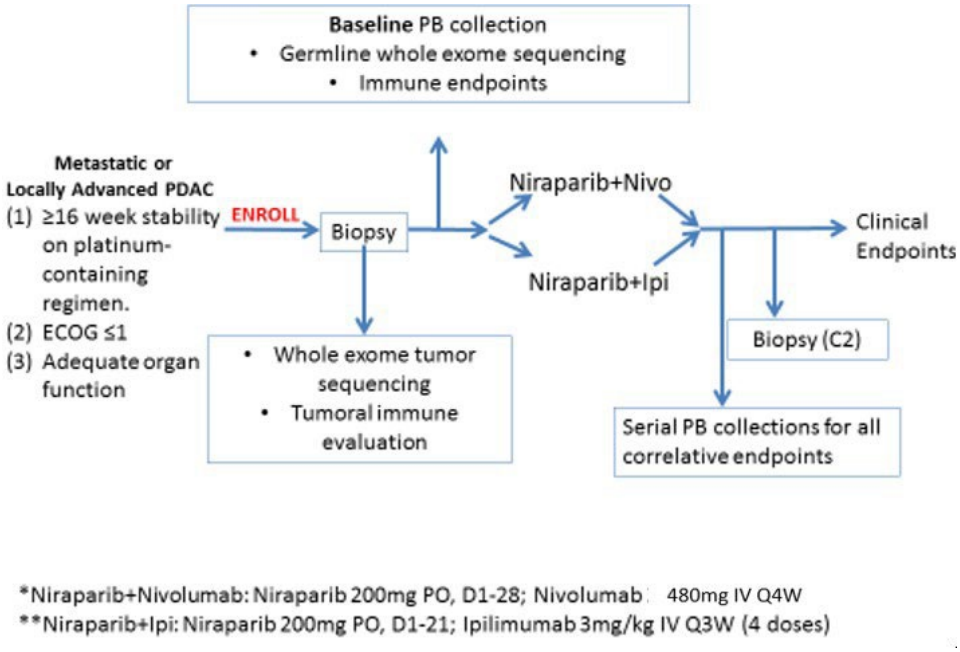
Assessments at this visit will include AEs, ECOG performance status, concomitant medications and procedures, physical examination, vital signs and weight measurements, hematology and serum chemistry, serum pregnancy for women of childbearing potential, CA 19-9 measurement, research blood sample for research analyses, whole blood sample for cytogenetic analysis, disease status assessment and study drug accountability.

4.1.4 Follow Up Phase

Patients who received nivolumab (Arm A) will have a 100 day follow-up period for AEs following the last dose of study treatment. Patients who received ipilimumab (Arm B) will have a 90-day follow-up period for AEs following the last dose of study treatment. Please refer to the study calendar for details.

CT scans at 30-day follow-up should also be performed for patients who discontinued treatment for reason other than disease progression and did not have a radiologic assessment at the End of Treatment visit. After the 30-day follow-up visit, patients will be followed for until 90, or 100 days post treatment depending on drugs administered and then for adverse events of special interests and survival annually until death, loss to follow-up, withdrawal of consent or until 5 years have passed, whichever occurs first.

4.1.5 Study Schema



*Niraparib+Nivolumab: Niraparib 200mg PO, D1-28; Nivolumab 480mg IV Q4W
**Niraparib+Ipi: Niraparib 200mg PO, D1-21; Ipilimumab 3mg/kg IV Q3W (4 doses)

4.1.6 End of Study

The trial will be completed when the last subject completes the last study-related phone call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary study endpoint will be progression-free survival at 6 months (PFS6) defined as the time from randomization to the occurrence of disease progression according to RECIST v1.1, as assessed by the investigator, or death from any cause. Patients who are alive and progression-free

will be censored on the most recent date that documents progression-free status (i.e. scan date or clinic visit date). The PFS6 will be determined from the Kaplan-Meier curve.

Evaluation of safety and tolerability of this combination as determined by CTCAE v5.0.

4.2.2 Secondary Study Endpoints

The secondary endpoints include:

- Evaluation of safety and tolerability of this combination as determined by CTCAE v5.0.
- Identification of HRDs and allele specific LOH in patients who have achieved stability on platinum-based therapy via whole exome sequencing.
- Correlation of HRDs with response to treatment with niraparib plus immune checkpoint blockade.
- Correlation of immune activity prior to and during therapy with response to treatment with niraparib and immune checkpoint blockade therapy.
- Overall response rate (ORR) by RECIST v.1.1 in those with measurable disease.
- Duration of response (DOR) as defined by the time from first documentation of complete or partial response by RECIST v.1.1 to date of disease progression or death due to any cause. Responders who have not progressed will be censored on the most recent date that documents progression-free status.
- Overall survival (OS) as defined by the time from start of study therapy to death due to any cause. Patients who are alive will be censored on the most recent date of patient contact.
- The incidence of adverse events (AEs), clinical laboratory abnormalities and dose modifications.

5 STUDY POPULATION AND DURATION OF PARTICIPATION

5.1 Inclusion Criteria

Eligible patients must meet the following inclusion criteria:

- Histologically or cytologically confirmed diagnosis of pancreatic adenocarcinoma with locally advanced or metastatic disease
- ≥18 years of age.
- Patients must be able to understand the study procedures and agree to participate in the study by providing written informed consent
- Patients must have received treatment with platinum-based (cisplatin, oxaliplatin or carboplatin) treatment for locally advanced or metastatic pancreatic cancer and have received a minimum of 16 weeks of therapy without evidence of disease progression based on the investigator's opinion. This does not have to be the patient's current treatment.

– Note: This requires at least stable imaging and a stable or decreasing tumor marker as applicable and as determined by the investigator.

– If a patient has demonstrated a biochemical and imaging response to platinum therapy and has not progressed within 16 weeks of starting this therapy but had to discontinue platinum prior to 16 weeks for a legitimate medical reason (as determined by the investigator), the patient may still be considered for the trial

- Patients may have previously failed non-platinum containing therapy or may never have previously progressed on treatment.

  – Discontinuation of the platinum component of the regimen for chemotherapy-related toxicity is permissible provided the patient has previously received at least 16 weeks of platinum-based therapy without evidence of disease progression ≤8 weeks after treatment with the platinum agent

- Measurable disease is not a requirement for study entry.
- Female participant has a negative serum pregnancy test within 24 hours prior to taking study treatment if of childbearing potential and agrees to abstain from activities that could result in pregnancy from screening through 6 months after the last dose of study treatment, or is of nonchildbearing potential (see Section 5.3).
- Male patient agrees to use an adequate method of contraception starting with the first dose through 90 days after the last dose of study treatment (see Section 5.3).
- Adequate organ function confirmed by the following laboratory values obtained ≤7 days prior to the first day of study therapy:

  – Absolute neutrophil count (ANC) ≥1.5 x 10^9/L

  – Platelets>100 x 10^9/L

  – Hemoglobin ≥9g/dL

  – Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN); if liver metastases, then ≤5 x ULN

  – Total bilirubin ≤1.5 x ULN; if liver metastases or metabolic disorder such as Gilbert's syndrome, then ≤2.5 x ULN.

  – Serum creatinine ≤1.5 x ULN or estimated glomerular filtration rate (GFR) ≥45 mL/min using Cockcroft Gault formula.

- Eastern Cooperative Oncology (ECOG) performance status of 0 to 1.

5.2 Exclusion Criteria

Patients will be excluded from participation if any of the following criteria apply:

- Prior treatment with a PARP inhibitor, ipilimumab, nivolumab or other cytotoxic T-lymphocyte-associated protein (CTLA-4), PD-1 or PD-L1 inhibitor.

- Patients who have demonstrated resistance to platinum agents (e.g. oxaliplatin, cisplatin) are not eligible to participate in this study
- Clinical evidence of uncontrolled malabsorption and/or any other gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with the absorption of niraparib
- Acute infection requiring intravenous antibiotics, antiviral or antifungal agents during the 14 days prior to first dose of study therapy
- Patients will be excluded if they have an active, known or suspected autoimmune disease, defined as: patients with a history of inflammatory bowel disease are excluded from this study, as are patients with a history of symptomatic autoimmune disease (e.g. rheumatoid arthritis, systemic progressive sclerosis (scleroderma), systemic lupus erythematosus, autoimmune vasculitis e.g. Wegener's Granulomatosis); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome).

  NOTE: Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.
- Has a history of interstitial lung disease or active, non-infectious pneumonitis
- Has received a live vaccine within 4 weeks prior to the first dose of trial therapy

  (Note: seasonal influenza vaccines for injection are generally inactivated and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed).
- For fertile patient (female able to become pregnant or male able to father a child), refusal to use effective contraception during the period of the trial and:

  – Female patients refusing to use effective contraception for 6 months after the last dose of study drug.

  – Male patients refusing to use effective contraception for 90 days after the last dose of study drug.
- Received any systemic treatment for pancreatic cancer ≤14 days prior to first dose of therapy. Patients must not have had investigational therapy administered ≤ 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study
- Patients will be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses >10mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Patient has had any known Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment.

- Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤21 days, prior to the first dose of therapy; in all cases, patients must be sufficiently recovered and stable before treatment administration.
- Active drug or alcohol use or dependence that would interfere with study compliance.
- Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.
- Patient must not have any known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)
- Patients must not be simultaneously enrolled in any therapeutic clinical trial
- Patients must not have had radiotherapy within 4 weeks of the first dose of study treatment
- Patients must not have a known hypersensitivity to the components of niraparib or the excipients
- Patients must not have received a transfusion (platelets or red blood cells) ≤ 4 weeks of the first dose of study treatment
- Patients must not be undergoing treatment for an active cancer at the time of randomization. Exceptions include: local therapies for skin cancers and hormonal therapies for breast or prostate cancer who have no evidence of active disease.
- Patients must not have a history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS), and must not test positive for HIV during study screening.
- Patients must not have known, symptomatic brain or leptomeningeal metastases

5.3 Patients or Partners of Patients with Reproductive Potential

Niraparib, nivolumab and ipilimumab should not be used during pregnancy or in women of childbearing potential not using reliable contraception.

Women of childbearing potential (WOCBP) should not become pregnant while on niraparib, nivolumab or ipilimumab and may not be pregnant at the beginning of treatment.

Pregnancy Testing: A pregnancy test should be performed on all WOCBP within 3 days prior to treatment.

Contraception: WOCBP must use effective contraception during niraparib, nivolumab and ipilimumab therapy and for 6 months after receiving the last dose of study treatment.

Acceptable methods of birth control include:

- Two highly effective forms of contraception, defined as contraceptive methods with a failure rate of less than 1% per year when used consistently and correctly. Patients and

their sexual partners who've undergone vasectomy or tubal occlusion must also use a male condom with spermicide.

- Permanent sterilization, defined as hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral orchidectomy
- Postmenopausal, defined as a female patient or sexual partner >45 years of age who has not menstruated for at least 12 consecutive months
- Total sexual abstinence

Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 90 days after the last dose of study treatment.

Patients must not breast-feed from the first dose of study drug and for 30 days following the final dose of niraparib or 3 months following the final dose of ipilimumab.

5.4 Total Number of Subjects and Sites

A total of 84 evaluable subjects will be enrolled at the University of Pennsylvania.

5.5 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

6 STUDY INTERVENTION

Oral niraparib plus either intravenous ipilimumab or intravenous nivolumab

6.1 Description

6.1.1 Niraparib

For complete details regarding Niraparib, please refer to the Investigator's Brochure.

Niraparib starting dose will be 200mg PO daily.

Niraparib is an orally available, selective PARP1 and -2 inhibitor.

The chemical name for niraparib is 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1). The empirical molecular formula for niraparib is C26H30N4O5S and its molecular weight is 510.61.

Niraparib tosylate monohydrate drug substance is a white to off-white, non-hygroscopic crystalline solid. Niraparib solubility is pH independent below the pKa of 9.95, with an aqueous free base solubility of 0.7 mg/mL to 1.1 mg/mL across the physiological pH range.

Niraparib is supplied in HDPE bottles with child resistant closures.

Niraparib does not contain gluten.

6.1.2 Nivolumab

For complete details regarding nivolumab, please refer to the Investigator's Brochure and FDA approved label.

Nivolumab dose will be 480mg IV every four weeks over a 30 minute period. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5mn/+10min).

Nivolumab, also referred to as BMS-936558-01 or BMS-936558, is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. The physical and chemical properties of nivolumab are provided below.

BMS Number	BMS-936558-01
Other Names	Nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1
Molecular Weight	146,221 daltons (143,619.17 daltons, protein portion)
Appearance	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present
Solution pH	5.5 to 6.5

Nivolumab Injection, 100 mg/10 mL (10 mg/mL)

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween© 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

Drug Product Preparation: Nivolumab Injection, 100 mg/10 mL (10 mg/mL). Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, pharmacy manual, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

6.1.3 Ipilimumab

For complete details regarding ipilimumab, please refer to the Investigator's Brochure and FDA approved label.

Ipilimumab dose will be 3mg/kg IV every 3 weeks over a 30-minute period. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5mn/+10min).

Ipilimumab (BMS-734016, MDX-010) is a fully human IgG1κ consisting of 4 polypeptide chains; 2 identical heavy chains primarily consisting of 447 amino acids each with 2 identical kappa light chains consisting of 215 amino acids each linked through inter-chain disulfide bonds. The physical and chemical properties of ipilimumab drug substance are provided in the table below.

BMS Number	734016
Molecular Weight	147,991 Daltons
Appearance	Clear to slightly opalescent, colorless to pale yellow liquid, may contain particles
Solution pH	7.0
pI	The isoelectric focusing analysis generates a banding pattern in the pI range of 8.5 to 8.8, with the major isoform at an approximate pI of 8.7.

Ipilimumab injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, non-pyrogenic, single-use, isotonic aqueous solution that may contain particles. Ipilimumab injection, 50 mg/10 mL or 200 mg/40 mL, is supplied in 10-cc or 50-cc Type I flint glass vials, respectively, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5 mg/mL at a pH of 7.0.

6.1.4 Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab

Long infusion times place a burden on patients and treatment centers. It is now established that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30 minutes' duration. This will limit the burden to patients.

Previous clinical studies of nivolumab and ipilimumab monotherapies and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab and a 90-minute infusion duration for ipilimumab (1 - 3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration (i.e., 60 minutes). However, recent data has shown that ipilimumab can be safely administered over a 30 minute period with acceptably low incidence of infusion related reactions [16].

Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over a long treatment duration. In subjects with advanced/metastatic clear cell RCC, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1/2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration.

Overall, a change in safety profile is not anticipated with 30-minute infusions of nivolumab, or ipilimumab.

6.2 Intervention Regimen

6.2.1 Niraparib + Nivolumab (Arm A)

Niraparib 200mg PO daily on days 1-28 of each 28-day cycle.

Nivolumab 480mg IV day 1 of each cycle

6.2.2 Niraparib + Ipilimumab (Arm B)

Niraparib 200mg PO daily on days 1-21 of each 21-day cycle.

Ipilimumab 3mg/kg IV day 1 of each cycle, for the first 4 cycles only.

6.2.3 DLT Definition and De-Escalation Decision Process (for Phase I Portion)

For Arm A and Arm B, dose limiting toxicities (DLTs) will be defined by toxicity occurring during the first 3 weeks of the study. A DLT will be considered as any non-hematologic AE of Grade 3 or higher that is at least possibly treatment-related with the exception of Grade 3 or higher nausea and vomiting which have not been treated with optimal anti-emetic therapy or Grade 3 or higher hypertension that has not been treated with optimal anti-hypertensive therapy.

The following hematologic DLT will be considered if any occurs in the first cycle:

- A grade 4 neutropenia lasting >7 days
- Febrile neutropenia
- Platelet count of <10,000/mm^3

Any DLT that causes a patient to miss >28 consecutive days of niraparib therapy will result in the patient being taken off treatment.

Cohort Expansion and Dose Reduction For Arm A or Arm B: If a DLT is observed in 1 or fewer patients in the first cohort of 3 patients, an additional 3 patients will be enrolled on that arm. If a DLT occurs in 2 or more patients within that cohort, then the dose of niraparib will be lowered as according to the table below. If <2/6 subjects experience a DLT, then this dose will then be declared as the MTD. No dose escalations are planned. Patients will be evaluable for toxicity if they have taken at least one dose of niraparib.

Table 1. Phase IB Portion: Niraparib Criteria for Dose De-Escalation and Cohort Size

Number of patients with DLT	Rule
0-1/3 DLT	Increase cohort to 6 patients
≥2/3 DLT	De-escalate dose, enroll 6 patients
If the cohort size is increased to 6 patients, the following rules apply	
Number of patients with DLT	**Rule**
<1/6 DLT	Current dose is the MTD
≥2/6 DLT	De-escalate dose, enroll 6 patients

6.2.4 Starting Dose and Dose Modifications of Protocol-Specified Treatment

6.2.4.1 Niraparib

The starting dose of niraparib will be 200mg PO daily on days 1-28 of each 28-day cycle (Arm A) and 200mg PO daily on days 1-21 of each 21-day cycle (Arm B).

Table 2. Recommended Niraparib Dose Reductions for Adverse Reactions

Dose Level	Dose
Starting Dose	200mg/day
First (and only) Dose Reduction	100mg/day

Refer to Section 6.2.5.1 for specific instructions regarding Niraparib dose modifications. Patients may not re-escalate once they have been dose reduced.

6.2.4.2 Nivolumab

The starting dose of nivolumab will be 480mg IV on day 1 of each 28 day cycle

There are no recommended dose reductions for nivolumab. Refer to Section 6.2.5.2 for specific instructions regarding when to hold and restart therapy for adverse reactions.

6.2.4.3 Ipilimumab

The starting dose of ipilimumab will be 3mg/kg IV on days 1 of each 21-day cycle.

There are no recommended dose reductions for ipilimumab. Refer to Section 6.2.5.2 for specific instructions regarding when to hold and restart therapy for adverse reactions.

6.2.5 Dose Modification Criteria and Criteria for Stopping Treatment

Dose adjustments are for AEs deemed related to the study medications. If, in the opinion of the treating Investigator, a toxicity is thought to be unrelated to study medications and resolves to a "Continue" or below lowest grade, no dose adjustments for the study medications are necessary.

For any toxicity leading to discontinuation of Niraparib, Nivolumab or Ipilimumab as described below, subjects may continue on the other study agent with approval of the PI.

For any toxicity (regardless of grade) that, despite optimal supportive care, is felt by the treating Investigator to present a risk to the patient safety, additional dose reduction, treatment delay, or treatment discontinuation is permitted at the discretion of the treating Investigator.

6.2.5.1 Niraparib Dose Modifications

Table 3. Niraparib Dose Modification for Non-hematologic Adverse Reactions

Non-hematologic CTCAE* ≥ Grade 3 treatment-related adverse reaction where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. Resume niraparib at a reduced dose as per Section 6.2.4.1. One dose reduction is permitted.
CTCAE ≥ Grade 3 treatment-related adverse reaction event lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue medication.

*CTCAE = Common Terminology Criteria for Adverse Events

Table 4. Niraparib Dose Modifications for Hematologic Adverse Reactions

Test complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time. Medical and supportive therapy should be optimized for management of toxicities.	
Platelet count <100,000/µL	First occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. Resume niraparib at same or reduced dose per Section 6.2.4.1. If platelet count is <75,000/µL, resume at a reduced dose.
	Second occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. Resume niraparib at a reduced dose. Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil <1,000/µL	Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/µL. Resume niraparib at a reduced dose. Discontinue niraparib if neutrophil level has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Hemoglobin <8 g/dL	Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until hemoglobin returns to ≥9 g/dL. Resume niraparib at a reduced dose. Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Hematologic adverse reaction requiring transfusion or hematopoietic growth factor support	For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Resume niraparib at a reduced dose.
Confirmed diagnosis of MDS* or AML†	Permanently discontinue niraparib.

*MDS = myelodysplastic syndrome
†AML = acute myeloid leukemia

If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC also will be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume.

Any patient requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a dose reduction upon recovery if study treatment is resumed.

The patient must be referred to a hematologist for further evaluation (1) if frequent transfusions are required or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less after 4 weeks.

For major surgery while on treatment, up to 28 days of study treatment interruption is allowed.

Once the dose of study treatment has been reduced, any re-escalation must be discussed with the medical monitor.

All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded.

6.2.5.2 Nivolumab and Ipilimumab Dose Modifications

Table 5. GI Adverse Event Management Algorithm for Nivolumab and Ipilimumab

Grade of Diarrhea/Colitis (CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: <4 stools/day over baseline Colitis: asymptomatic	• Continue immunotherapy (I-O) per protocol • Symptomatic treatment	• Close monitoring for worsening of symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Hold I-O therapy • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Table 6. Renal Adverse Event Management Algorithm for Nivolumab and Ipilimumab

Grade of Creatinine Elevation (CTCAE v5)	Management	Follow-Up
Grade 1 Creatinine >ULN and > than baseline but ≤1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline:</u> • Resume routine creatinine monitoring per protocol <u>If worsens:</u> • Treat as Grade 2 or 3-4
Grade 2-3 Creatinine > 1.5x baseline to ≤6x ULN	• Hold I-O therapy • Monitor creatinine every 2-3 days • 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, resume I-O therapy and routine creatinine monitoring per protocol. <u>If elevations persist> 7 days or worsen:</u> • Treat as Grade 4
Grade 4 Creatinine >6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrology • Consider renal biopsy	<u>If returns to Grade 1:</u> • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections.

Table 7. Pulmonary Adverse Event Management Algorithm for Nivolumab and Ipilimumab

Grade of Pneumonitis (CTCAE v5)	Management	Follow-Up
Grade 1 Radiographic changes only	• Consider holding I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Hold I-O therapy • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0mg/kg/day methylprednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Table 8. Hepatic Adverse Event Management Algorithm for Nivolumab and Ipilimumab

Grade of Liver Test* Elevation (CTCAE v5)	Management	Follow-Up
Grade 1 AST or ALT >ULN – 3x ULN and/or T.bili >ULN – 1.5x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 AST or ALT > 3x to ≤5x ULN and/or T.bili >1.5 to ≤ 3x ULN	• Hold I-O therapy • Increase frequency of monitoring to every 3 days	If returns to baseline: • Resume routine monitoring, resume I-O therapy per protocol If elevation persists >5-7 days or worsens: • 0.5-1mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 months, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5x ULN or T.bili >3x ULN	• Discontinue I-O therapy** • Increase frequency of monitoring to every 1-2 days • 1.0-2.0mg/kg/day methylprednisolone IV or IV equivalent*** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least one month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines.

* Exceptions/Notes:

- If a subject has a baseline AST or ALT thatis within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity (2 grade shift)
- If a subject has baseline AST or ALT within the Grade 1 toxicity range, delay dosing for drug-related Grade≥ 3 toxicity (2 grade shift)
- If a subject has baseline AST or ALT within the Grade 2 toxicity range, delay dosing for a two-fold drug-related increase in AST or ALT or for AST or ALT values 8x ULN (whichever is lower).

**I-O therapy may be delayed rather than discontinued if AST/ALT ≤8x ULN or T.bili ≤5x ULN
***The recommended starting dose for grade 4 hepatitis is 2mg/kg/day methylprednisolone IV.

Table 9. Endocrinopathy Management Algorithm for Nivolumab and Ipilimumab

<table>
<tr><td>Asymptomatic TSH Elevation</td><td colspan="2">• Continue I-O therapy per protocol
• If TSH <0.5x LLN or TSH > 2x ULN, or consistently out of range in 2 subsequent measurements: include fT4 at subsequent cycles as clinically indicated; consider endocrinology consult</td></tr>
<tr><td>Symptomatic Endocrinopathy</td><td>• Evaluate endocrine function
• Consider pituitary scan

<u>Symptomatic with abnormal labs/pituitary scan:</u>
• Hold I-O therapy
• 1-2mg/kg/day methylprednisolone IV or PO equivalent
• Initiate appropriate hormone therapy

<u>No abnormal lab/pituitary MRI scan but symptoms persist:</u>
• Repeat labs in 1-3 weeks/MRI in 1 month</td><td><u>If improves (with or without hormone replacement):</u>
• Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
• Resume I-O therapy per protocol
• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component</td></tr>
<tr><td>Suspicion of Adrenal Crisis (eg severe dehydration, hypotension, shock out of proportion to current illness)</td><td colspan="2">• Hold or discontinue I-O therapy per protocol
• Rule out sepsis
• Stress dose IV steroids with mineralocorticoid activity
• IV fluids
• Consult endocrinologist
• If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy</td></tr>
</table>

Table 10. Skin Adverse Event Management Algorithm for Nivolumab and Ipilimumab

Grade of Rash (CTCAE v5)	Management	Follow-Up
Grade 1-2 Covering ≤30% BSA*	• Symptomatic therapy (e.g. antihistamines, topical steroids) • Continue I-O therapy per protocol	<u>If persists >1-2 weeks or recurs:</u> • Consider skin biopsy • Delay I-O therapy per protocol • Consider 0.5-1.0mg/kg/day methylprednisolone IV or oral equivalent. Once improved, taper steroids over at least 1 months, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. <u>If worsens:</u> • Treat as Grade 3-4
Grade 3-4 Covering >30% BSA; Life threatening consequences	• Hold or discontinue I-O therapy per protocol • Consider skin biopsy • Dermatology consult • 1.0-2.0mg/kg/day IV methylprednisolone or IV equivalent	<u>If improves to Grade 1:</u> • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol

*Refer to NCI CTCAE v5 for term-specific grading criteria

Table 11. Neurological Adverse Event Management Algorithm for Nivolumab and Ipilimumab

Grade of Neurological Toxicity (CTCAE v5)	Management	Follow-Up
Grade 1 Asymptomatic or mild symptoms; intervention not indicated	• Continue I-O therapy per protocol	• Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; limiting instrumental ADLs	• Hold I-O therapy • Treat symptoms per local guidelines • Consider 0.5-1.0mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: • Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0mg/kg/day IV or IV equivalent methylprednisolone • Add prophylactic antibiotics or opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens of atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Hepatic Impairment (Ipilimumab):

Clearance (CL) of ipilimumab in subjects with mild and moderate hepatic impairment was similar to that of subjects with normal hepatic function.

Hepatic Impairment (Nivolumab):

No clinically important differences in the CL of nivolumab were found between subjects with mild hepatic impairment and normal hepatic function.

Renal Impairment (Nivolumab):

No clinically important differences in the CL of nivolumab were found between subjects with mild or moderate renal impairment and subjects with normal renal function.

6.2.6 Treatment Beyond Progression

If the patient has met criteria for radiologic progression by RECIST v1.1, but the patient is still receiving benefit from study therapy (e.g., patient has mixed radiologic response or is continuing

to have symptomatic benefit without decline in performance status) according to the Investigator, then continuation of treatment will be considered. In such cases, the decision to continue will be made by the Investigator, and must be documented prior to continuing treatment with study treatment. Patients will continue to have all protocol-required assessments specified in the Schedule of Assessments Table. Treatment must be discontinued when the patient is no longer benefiting from therapy, as per the Investigator.

6.3 Prior and Concomitant Therapies

Patients who have received prior treatment with PARP inhibitors and/or immune checkpoint inhibitors are not eligible to participate in this study. Patients who have demonstrated resistance of their pancreatic adenocarcinoma to platinum agents (e.g. oxaliplatin, cisplatin) are not eligible to participate in this study.

During the study, supportive care (e.g., antiemetics; analgesics of pain control) may be used at the investigator's discretion and in accordance with institutional procedures.

All procedures performed (e.g., thoracentesis, paracentesis etc.) and medications used during the study must be documented on the electronic case report form (eCRF).

6.3.1 Anticancer or Experimental Therapy

No other concomitant therapies for pancreatic cancer (including chemotherapy, radiation, hormonal treatment, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is participating in the study.

Ongoing therapies for previously treated non-pancreatic cancer (e.g., hormonal treatment for prior breast cancer) are permitted. The data on niraparib in combination with cytotoxic medicinal products are limited. Therefore, caution should be taken if niraparib is used in combination with other cytotoxic medicinal products.

Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing > 20% of the bone marrow within 4 weeks of the first dose of study treatment) is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.

6.3.2 Hematopoietic Growth Factors and Blood Products

Hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines. Prophylactic cytokine (Granulocyte Colony-Stimulating Factor [GCSF]) administration should not be given in the first cycle of the study, but may be administered in subsequent cycles according to local guidelines and Section 6.2.5.1.

6.3.3 Bisphosphanates

Bisphosphanates are permitted.

6.3.4 Anticoagulants

Anticoagulants are permitted.

6.3.5 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions.

6.3.6 Substrates of P-glycoprotein

Niraparib weakly induces Cytochrome P450 (CYP)1A2 in vitro and is a relatively poor substrate for P-glycoprotein (P-gp); therefore, investigators are advised to use caution with the substrates for CYP1A2 with a narrow therapeutic range, i.e. theophylline and tizanidine. The niraparib safety profile includes risk for thrombocytopenia; therefore, patients should be advised to use caution with anticoagulation and antiplatelet drugs.

6.3.7 Vaccines

The combination of niraparib with vaccines or immunosuppressant agents has not been studied.

6.3.8 Blood Donation

Patients must not donate blood during the study or for 90 days after the last dose of study treatment.

6.4 Warnings and Precautions

6.4.1 Niraparib

6.4.1.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

MDS/AML, including cases with fatal outcome, have been reported in a small number of patients who received niraparib or placebo. In the Phase 3 NOVA trial, the incidence of MDS/AML in patients who received niraparib (1.4%) was similar to that seen in patients who received placebo (1.1%). The duration of niraparib treatment in patients prior to developing MDS/AML varied from 1 month to >2 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received multiple platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with niraparib, then niraparib should be permanently discontinued.

6.4.1.2 Hypertension, including Hypertensive Crisis

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Pre-existing hypertension should be adequately controlled before starting niraparib treatment. Blood pressure and heart rate should be monitored at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with niraparib.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the niraparib dose, if necessary. In the clinical program, blood pressure

measurements were obtained on Day 1 of each 28-day cycle while the patient remained on niraparib. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without niraparib dose adjustment. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

6.4.1.3 Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports (0.09% of clinical trial patients) of niraparib-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES). PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinstating niraparib therapy in patients previously experiencing PRES is not known.

6.4.1.4 Embryo-fetal Toxicity

No embryo-fetal toxicity study has been performed. Based on its mechanism of action, niraparib could cause embryonic or fetal harm when administered to a pregnant woman. Refer to Section 5.3.

6.4.1.5 Pregnancy and Contraception

Refer to Section 5.3.

6.4.1.6 Overdosage

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study treatment that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on a Special Situations Report Form or its designated representative, within 24 hours. An overdose should be reported even if it does not result in an AE.

There is no specific treatment in the event of niraparib overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

6.4.1.7 Other Potential Risks of Niraparib

The following adverse reactions (all CTCAE grades) have been reported in ≥20% of patients who received niraparib: anemia, thrombocytopenia, nausea, constipation, vomiting, fatigue, platelet count decreased, decreased appetite, headache, and insomnia. The median exposure to niraparib in these patients was 250 days.

The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 367 patients receiving niraparib: neutropenia, palpitations, asthenia, neutrophil count decreased, dizziness, dysgeusia, dyspnea, cough and hypertension. The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients

receiving niraparib: tachycardia, dry mouth, mucosal inflammation, white blood cell count decreased, aspartate aminotransferase increased, alanine aminotransferase increased and photosensitivity reaction.

6.4.2 Nivolumab

6.4.2.1 Overdosage

There is no available information concerning overdose with nivolumab. Depending on the symptoms and/or signs leading to the suspicion of overdose, supportive medical management should be provided. There is no specific antidote.

6.4.2.2 Pulmonary Adverse Events

Pulmonary AEs have been observed following treatment with nivolumab. The frequency of pulmonary AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. The majority of cases reported were Grade 1 or 2, and subjects presented with either asymptomatic radiographic changes (e.g., focal ground glass opacities and patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3 or 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. Pulmonary AEs have been reported in subjects with a variety of tumor types; however, there have been numerically more cases in subjects with NSCLC. It is not clear whether the underlying NSCLC is a distinct risk factor, or if subjects with NSCLC are more likely to develop radiographic changes and symptoms for which it is difficult to distinguish between nivolumab-related and unrelated causes. At this time, no other underlying risk factor, including prior radiotherapy, presence of lung metastases, or underlying pulmonary medical history, has yet to be identified.

Asymptomatic subjects were typically managed with dose delay. Subjects with Grade 2 pneumonitis were managed with dose delay, treated with corticosteroids, and had resolution of pneumonitis within days to weeks. In cases where nivolumab treatment was restarted, recurrence of pneumonitis was infrequently reported across the nivolumab program. Subjects with more severe cases of pneumonitis can be difficult to treat. In a few cases, subjects who did not initially respond to corticosteroids were administered anti-tumor necrosis factor therapy (infliximab) and/or cyclophosphamide. In some of these cases, pneumonitis began to resolve following the use of these additional therapies.

Guidelines on the recommended management of pneumonitis and other pulmonary AEs are found in Table 7. Early recognition and treatment of pneumonitis is critical to its management. Subjects should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms. As respiratory symptoms are common in subjects with cancer (e.g., NSCLC), it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., infection or progression of disease) and a possible drug-related pulmonary toxicity as the management of these events can be quite different. For symptomatic nivolumab-related pneumonitis, the principal treatment is corticosteroids Table 7. All subjects with Grade 3-4 pneumonitis should discontinue nivolumab and initiate treatment with high doses of corticosteroids.

6.4.2.3 Gastrointestinal Adverse Events

Gastrointestinal AEs have been observed following treatment with nivolumab. Most cases of diarrhea were of low grade (Grade 1-2). Colitis occurred less frequently than diarrhea. High-grade cases of diarrhea and colitis were managed with corticosteroids and, in all cases, the events resolved.

The recommended management of GI AEs is provided in Table 5. Early recognition and treatment of diarrhea and colitis are critical to their management. Subjects should be advised to seek medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. As GI symptoms are common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., infection or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade GI AEs is corticosteroids Table 5. Caution should be taken in the use of narcotics in subjects with diarrhea, colitis, or abdominal pain as pain medicines may mask the signs of colonic perforation.

Diverticular Perforation: The prevalence of diverticulosis in the general population is common and increases with age from 10% under 40 years of age to approximately 50% over 60 years of age. Approximately 10% to 25% of subjects with diverticulosis develop diverticulitis. Perforation occurs in 50% to 70% of instances of complicated diverticulitis. Corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics are known risk factors for diverticular perforation. Given the high prevalence of diverticulosis and diverticulitis in the general population, it is expected that some nivolumab-treated subjects will have these conditions concurrently with their malignancy. Cases of diverticular perforation while on concomitant corticosteroids (6 cases) or NSAID (1 case) were observed in nivolumab program. While there is insufficient evidence to suggest that diverticulosis or diverticulitis is a predisposing factor for GI perforation following nivolumab administration, clinical caution should be exercised, as appropriate, for subjects on concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, be vigilant for signs and symptoms of potential perforation, especially in subjects with known diverticular disease.

6.4.2.4 Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, DILI, have been observed following treatment with nivolumab and nivolumab in combination with ipilimumab. Most cases were of low or moderate grade. Higher-grade hepatic AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved.

The recommended management of hepatic AEs is provided in Table 8 . Early recognition and treatment of elevated LFTs and DILI are critical to their management. Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each nivolumab treatment. As LFT abnormalities are common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., infection, progression of disease, concomitant medications, or alcohol) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade hepatic AEs is corticosteroids (Table 8).

6.4.2.5 Endocrinopathies

Endocrinopathies have been observed following treatment with nivolumab. Most cases were of low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (e.g., TSH) or as part of a work-up for associated symptoms (e.g., fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (e.g., hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Moderate- to high-grade cases were managed with hormone replacement therapy and, in some cases, with the addition of corticosteroids. In some cases, nivolumab treatment was held until adequate hormone replacement was provided.

Guidelines on the recommended management of endocrinopathies are provided in Table 9. Early recognition and treatment of endocrinopathies are critical to its management. Subjects should be advised to seek medical evaluation if they notice new-onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens. As fatigue is common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., progression of disease, anemia, concomitant medications, or depression) and a possible drug-related AE as the management can be quite different. The principal management of endocrinopathies is hormone replacement therapy. For subjects with moderate- or high-grade events, corticosteroids may also be used.

6.4.2.6 Skin Adverse Events

Rash and pruritus were the most common skin AEs observed following treatment with nivolumab. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids.

Subjects should be advised to seek medical evaluation if they notice new-onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash, or if there is any unusual appearance or clinical feature associated with it. Other drugs that may cause rash should be considered in the differential and, if possible, discontinued. In addition, careful evaluation of potential benefit-risk is necessary when considering the use of nivolumab or ipilimumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior immune-stimulating therapy.

Guidelines on the recommended management of skin AEs are provided in Table 10. The principal treatment for skin AEs, such as rash and pruritus, consists of symptomatic management. Topical corticosteroids can be used for low- to moderate-grade focal rash. Systemic corticosteroids should be used for diffuse and high-grade rash. Rare cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been observed. If symptoms or signs of SJS or TEN appear, nivolumab or nivolumab in combination with ipilimumab should be withheld and the patient referred for specialized care for assessment and treatment. If the patient has confirmed SJS or TEN, permanent discontinuation of nivolumab or nivolumab in combination with ipilimumab is recommended.

6.4.2.7 Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. The frequency of renal AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. Most cases were Grade 2 or 3 and based on creatinine elevation. Subjects with a history of RCC or prior nephrectomy did not appear to be at higher risk. Events were managed with corticosteroids and, in all cases, renal function partially or fully improved.

The recommended management of renal AEs is provided in Table 6. Physicians should monitor creatinine regularly. As creatinine abnormalities are common in subjects with cancer and other comorbidities, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., dehydration, concomitant medications, hypotension, or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for renal AEs is corticosteroids (Table 6).

6.4.2.8 Neurological Adverse Events

Neurologic AEs have been uncommonly observed following treatment with nivolumab. The frequency of neurologic AEs may be greater with nivolumab + ipilimumab combination therapies than with nivolumab monotherapy or other nivolumab combinations. Neurologic AEs can manifest as central abnormalities (e.g., aseptic meningitis, encephalopathy, or encephalitis) or peripheral sensory/motor neuropathies (e.g., Guillain-Barre Syndrome, myasthenia gravis complicated with sepsis and fatality). The onset has been observed as early as after a single treatment with the nivolumab + ipilimumab combination.

The recommended management of neurologic AEs is provided in Table 11. Early recognition and treatment of neurologic AEs is critical to its management. Subjects should be advised to seek medical evaluation if they notice impairment in motor function (e.g., weakness), changes in sensation (e.g., numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes. As neurologic symptoms can be common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., progression of disease, concomitant medications, or infection) and a possible drug-related AE as the management can be quite different. The principal treatments for neurologic toxicity are dose delay, corticosteroids, and IV immunoglobulin as outlined in the safety algorithm (Table 11). For high-grade related neurological AEs, nivolumab should be discontinued.

6.4.2.9 Infusion Reactions

Infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon. Investigators are advised to monitor for fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty in breathing during and immediately after administration of nivolumab. Study protocols provide explicit guidance on the management of infusion-related reactions.

6.4.2.10 Lipase/Amylase Elevations

Asymptomatic elevations in lipase and amylase have been reported. In monotherapy studies, lipase and amylase levels were not systematically monitored, so an estimate of the frequency of

asymptomatic lipase/amylase elevations is unknown. In studies evaluating the safety of the nivolumab + ipilimumab combination in multiple tumor types, lipase and amylase levels were systematically monitored, and elevations in any grade of lipase/amylase were consistently noted in approximately 10% to 30% of subjects. Very few subjects reported associated symptoms (e.g., abdominal pain) or radiographic findings (e.g., stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values.

As lipase/amylase abnormalities are not uncommon in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., progression of disease, concomitant medications, or alcohol) and a possible drug-related cause as the management can be quite different. The recommended management of nivolumab-related elevated lipase/amylase values centers around close observation. Physicians should ensure that subjects have no associated symptoms consistent with pancreatitis, such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low grade over the course of weeks, whether or not subjects receive corticosteroids. Asymptomatic elevations should be monitored approximately on a weekly basis, and nivolumab should be held per protocol instructions. For sustained asymptomatic Grade 4 elevations, nivolumab should be discontinued per protocol instructions. For subjects with elevated lipase/amylase and symptoms consistent with possible pancreatitis, nivolumab should be discontinued, and consultation with a gastroenterologist should be considered.

6.4.2.11 Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (e.g., uveitis) is an uncommon, but clinically important, event. Uveitis may occur more frequently with nivolumab + ipilimumab combination therapy than with nivolumab monotherapy or nivolumab in combination with other therapies. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Topical corticosteroids may be used to manage low-grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause.

6.4.2.12 Other Immune-mediated Adverse Events

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

6.4.3 Ipilimumab

Blockade of CTLA-4 by ipilimumab leads to T-cell activation, with the potential for clinical inflammatory AEs primarily involving the skin (dermatitis/pruritus), GI tract (diarrhea/colitis), liver (hepatitis), endocrine glands (e.g., hypophysitis and adrenal or thyroid abnormalities), and

other less frequent organs (e.g., uveitis/episcleritis). The majority of these inflammatory AEs initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab. The majority of the inflammatory AEs is reversible with the guidance issued below. In rare cases, these inflammatory AEs may be fatal.

Patients should be assessed for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy, and clinical chemistries (including liver function, adrenocorticotropic hormone [ACTH] level, and thyroid function tests) should be evaluated at baseline and before each dose of ipilimumab.

During evaluation of a suspected inflammatory AE, all efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes. Serological, immunological, imaging, and biopsy with histology (e.g., biopsy-proven lymphocytic) data should be used to support the diagnosis of an immune-mediated toxicity or support an alternative cause of the AE.

In general, for severe inflammatory AEs, ipilimumab should be permanently discontinued, and systematic high-dose corticosteroid therapy should be initiated. For moderate immune-mediated

AEs, ipilimumab should be held or delayed, and moderate-dose corticosteroids should be considered.

Based on limited current clinical experience, corticosteroids do not appear to adversely affect the anti-tumor response. For example, disease control was maintained in subjects with objective responses who received corticosteroid administration for concomitant serious inflammatory AEs.

The management guidelines for general inflammatory GI, liver, skin, endocrine, and neurological toxicities are provided in this Protocol in Section 6.2.

6.4.3.1 Gastrointestinal Toxicities

The most common site for ipilimumab-induced GI toxicity was the lower GI tract, and the most common presentation was mild to severe diarrhea or colitis with occasional bloody stools. In some cases, diarrhea began as mild and then worsened. Constipation was rarely associated with ipilimumab administration. Delay in corticosteroid treatment may be associated with a poor outcome for patients with high-grade diarrhea.

6.4.3.2 Liver Toxicities

Subjects receiving ipilimumab may develop elevations in LFTs in the absence of clinical symptoms. Occasionally, patients may present with symptoms, including right upper quadrant abdominal pain or unexplained vomiting. Most cases of inflammatory hepatitis responded to high-dose corticosteroids (IV route recommended).

All patients require close medical monitoring of LFTs and immediate intervention to prevent serious sequelae. LFTs should be routinely assessed and reviewed prior to administration of each dose of ipilimumab.

6.4.3.3 Endocrine Toxicities

The most common inflammatory endocrine toxicities occurring in ipilimumab-treated subjects are hypophysitis and hypopituitarism. Secondary cortisol deficiency (hypoadrenalism), hypothyroidism or thyroiditis, and, less commonly, other endocrinopathies may occur concomitantly with hypophysitis; however, these may also present as the only or as primary

endocrinopathy. Most patients with hypopituitarism presented with nonspecific complaints such as fatigue, visual field defects, confusion, or impotence. Some patients have had headache as the predominant presentation. The majority of subjects with hypopituitarism demonstrated enlarged pituitary glands based on brain magnetic resonance imaging (MRI). Low ACTH and cortisol were the most common biochemical abnormality; abnormal (mostly low) thyroid-stimulating hormone (TSH), free thyroxine (fT4), triiodothyronine (T3), testosterone, or prolactin have also been reported in some subjects. Symptoms of hypopituitarism and other endocrine toxicities were generally controlled with appropriate hormone replacement.

6.4.3.4 Skin Toxicities

The most common inflammatory skin toxicities occurring in ipilimumab-treated subjects are rash and pruritus, mostly mild to moderate in severity. Two cases of fatal treatment-related toxic epidermal necrolysis have been reported in clinical trials. Post-marketing surveillance identified a fatal toxic epidermal necrolysis event in one subject who received ipilimumab after experiencing a severe or life-threatening skin adverse reaction on a prior cancer immune-stimulating therapy. Caution should be used when considering the use of ipilimumab in patients who have previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune-stimulating therapy (CARES Database No. 21333844).

6.4.3.5 Neurological Toxicities

Neurological manifestations in subjects treated with ipilimumab may include motor and/or sensory neuropathy. Given the difficulty in definitely establishing an inflammatory etiology, alternative etiologies (e.g., tumor progression) should be excluded. Fatal Guillain-Barre syndrome and cases of myasthenia gravis have been reported in clinical trials of ipilimumab. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy should be evaluated, and non-inflammatory causes such as disease progression, infections, metabolic disorders, and medications should be excluded.

6.4.3.6 Other Toxicities

Ocular inflammation, manifested as Grade 2 or 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects (< 1%) and occasionally occurred in the absence of clinically apparent GI symptoms.

Other presumed inflammatory events reported include, but were not limited to, the following (individually reported for < 1% of subjects unless noted otherwise): arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, non-infective myocarditis, polymyositis, eosinophilia, pericarditis, urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, infusion reactions, and MG.

6.5 Receipt

Niraparib, nivolumab and ipilimumab will be received by the Investigational Drug Pharmacy at each clinical site.

6.6 Storage

6.6.1 Niraparib

Niraparib is supplied by TESARO in high-density polyethylene (HDPE) bottles with child-resistant plastic closures. The study treatment will be open-label and will not be participant-specific. Detailed information on the product can be found in the Niraparib Storage and Handling Guidelines.

All study treatment supplies must be stored in accordance with the manufacturer's instructions and package labeling. Until dispensed to the participants, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

6.6.2 Nivolumab

Nivolumab Injection, 40mg/Vial (10mg/mL), 100 mg/Vial (10 mg/mL), and 240mg/Vial (10mg/mL): Nivolumab Injection Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to up to 25°C, 77°F) and room light for up to 48 hours.

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container: The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and room light. The maximum 8 hours under room temperature and room light conditions includes the product administration period.

6.6.3 Ipilimumab

Ipilimumab Injection, 50mg/10mL (5 mg/mL) or 200 mg/40 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

Ipilimumab injection may be stored undiluted (5 mg/mL) or following dilution in 0.9% Sodium

Chloride Injection, or 5% Dextrose Injection in PVC, non-PVC/non-DEHP or glass containers for up to 24 hours (at 2°C to 8°C) or room temperature/room light.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

6.7 Administration and Accountability

Niraparib: An adequate quantity of niraparib will be provided to the patient to last until the next scheduled visit. Patients will be instructed to record daily doses taken or not taken in a provided institutional dosing diary, and will be instructed to bring their niraparib tablets, all containers (empty, partially used and/or unopened) and dosing diary to the next scheduled visit for reconciliation by site personnel. Food does not significantly affect the absorption of niraparib; therefore, niraparib may be taken without regard to meals. If a patient vomits or misses a dose of niraparib, an additional dose should not be taken. The next dose should be taken at the regularly scheduled time.

Ipilimumab and nivolumab are injectable drugs that will be administered in the clinic by research and clinical nursing staff.

6.8 Subject Compliance Monitoring

Documentation of dosing will be recorded in a study specific institutional dosing diary. Study site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets to be taken for each dose. Patients (or legally authorized representative) will be instructed to record dosing information for niraparib taken at home in the dosing diary and to bring the dosing diary and all unused tablets with them to scheduled clinic visits. A compliance check and tablet count will be performed by study personnel during clinic visits. Every effort should be made to ensure patients complete the dosing diary and return their study drug containers at the end of each cycle of treatment. In the event a patient has unused pills from the prior cycle, these may be re-dispensed. The coordinator will keep a record of returned pills and re-dispensed pills.

6.9 Return or Destruction of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed on-site in accordance with standard policies for the destruction of investigational agents with prior sponsor approval.

7 STUDY PROCEDURES

7.1 Schedule of Assessments- ARM A (Niraparib + Nivolumab)

All procedures and assessments are to be completed within ±3 days of the scheduled time point.

Table 12. Schedule of Assessments – Arm A

Procedure[a]	Day -28 to Day -1 (unless otherwise specified)	C1D1[b]	D1 of C2 and Beyond[y]	EOT	30 Day FU	100 Day FU	LTFU
Informed Consent	x						
Randomization	x						
Demographics/ Medical History[c]	x						
Physical Exam, Height[d], weight	x	X	x	x			
ECOG PS	x	X	x	x			
Vital Signs[e]	x	X	x	x			
Blood Pressure and heart rate Monitoring[w]		X	X				
Adverse Events[f]	x	X	x	x	x	x	
Prior/Concomitant Medications and Procedures	x	X	x	x			
Hematology[g]	x[h]	X	x	x			
Serum Chemistry[i]	x[h]	X	x	x			
Lipase	x	X	x	x			
Magnesium	x	X	x	x			
Phosphorus	x	X	x	x			
TSH (Thyroid Function)[j]	x	X	x	x			
HIV AB	x						

Procedure[a]	Day -28 to Day -1 (unless otherwise specified)	C1D1[b]	D1 of C2 and Beyond[y]	EOT	30 Day FU	100 Day FU	LTFU
CA 19-9 and/or CEA[t]		X	x	x			
Serum Pregnancy Test (WOCBP only)[k]	x	X	x	x			
Disease Assessment/ Tumor Scans[l]	x		X[m]	X[n]	x[o]		
Archival Tissue (If available[p])	x						
Tumor Tissue Biopsy (if safe/feasible)	X[q]		X[r]				
PBMC/Serum		X[x]	x[v]	X[v]			
Blood for WeS		X					
Blood for CTM		x[v]	x[v]	X[v]			
Niraparib Dispensation, Administration, Accountability		X	x	x			
Nivolumab Infusion		X	x				
Survival Status							X[s]
Follow-Up for MDS/AML							X[s]
Bone Marrow aspirate and biopsy sample[u]		X[u]					

ALP = alkaline phosphatase, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, BUN = blood urea nitrogen, CR = complete response, CT = computed tomography, hrs = hours, MRI = magnetic resonance imaging, PET = positron emission tomography, PK = pharmacokinetics, PR = partial response, SAE = serious adverse event, WBC = white blood cell, WOCBP = women of childbearing potential

a = Treatment cycles are 28 days. Unless otherwise specified, all assessments are to be completed within ±3 days of scheduled time point. Delay of treatment schedule up to 10 days, as allowed by the protocol, is permitted at the discretion of the treating Investigator with approval of the PI (e.g. toxicity, weather, vacation).

b = Any procedures required on Day 1 of Cycle 1 may be omitted if completed ≤3 days earlier during the screening period.

c = Patient's medical record must include prior treatments received, date of progression, and radiology and/or medical report(s) to support assessment of disease progression, and, if applicable, intolerable toxicity to chemotherapy.

d = Height at screening only

e = Vital signs (blood pressure, pulse, and temperature) to be taken pre-dose on clinic visit days. Blood pressure and heart rate should be monitored at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with niraparib.

f = AEs are recorded from the time of signing informed consent through 30 days after last dose of niraparib. Ongoing SAEs will be followed to resolution or until SAE stabilizes.
g = Includes hemoglobin, hematocrit, WBC and differential (with ANC) and platelet count. Blood will be analyzed by a local laboratory. **Weekly CBCs should be performed during the first four weeks of therapy.**
h = to be performed ≤7 days prior to the first dose of therapy or prior to dosing on day 1 to confirm eligibility
j = includes total protein, albumin, creatinine or estimated GFR using Cockgroft Gault formula, BUN, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, CO2, calcium, phosphorous, magnesium and lipase. Blood will be analyzed by a local laboratory.
j = If TSH is abnormal, fT4 and T3 will be drawn. The patient will be clinically managed for thyroid abnormalities at the discretion of the investigator.
k = Women of childbearing potential must have a negative serum pregnancy test result within 24 hours prior to the first dose of niraparib. A serum or urine pregnancy test (investigator's discretion) must be performed ≤3 days prior to Day 1 of every cycle during the treatment phase. A serum pregnancy test must be performed at the End of Treatment visit.
l = Disease assessment to include clinical examination, and appropriate imaging techniques, including CT scans of the chest, abdomen and pelvis, with appropriate slice thickness per RECIST; other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. The same method used to detect lesions at baseline is to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment.
m = Tumor scans to be performed within 7 days prior to start of every 2nd cycle (every odd numbered cycle), or approximately every 8 weeks. Please refer to footnote "y" for procedures for stable patients who are stable following 11 cycles of treatment
n = End of treatment CT scans should be performed if treatment was discontinued for reason other than radiologic disease progression and if previous tumor assessment scan was performed ≥8 weeks prior to EOT visit.
o = If CT scans were not performed at End of Treatment or within 28 days prior to End of Treatment, a CT scan should be performed at the 28-day follow-up visit.
p = Archival tumor tissue, if available, will be collected and stored. (Note: This sample is not required to be submitted on Cycle 1, Day 1, but should be submitted as soon as possible after a patient begins treatment).
q = A screening core tumor biopsy will be collected prior to C1D1 if deemed safe and feasible for those patients who pass the screening evaluation.
r = A core tumor biopsy will be performed during treatment at cycle 2 day 1 if deemed safe and feasible +/- 7 days
s = All patients discontinued from treatment, regardless of reason, should be followed annually until death, loss to follow-up, withdrawal of consent from study, five years, or closure of the study. Follow-up can be performed via telephone, email and/or office visit.
t = Whichever is appropriate for the patient. Patients with a prior history of both markers being elevated will have both drawn serially as per the study calendar.
u = For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria) and other sample testing results related to MDS/AML.
v = Blood samples for PBMC, Serum, and CTM will be collected according to the site lab manual at Cycle 1 and every other Cycle (every 8 weeks) starting with cycle 3 thereafter, and at EOT. For patients coming in every 12 weeks, PBMD, Serum and CTM will be collected at that visit.
w= blood pressure and heart rate should be monitored weekly for first 2 months, monthly for first year, and periodically thereafter
x= PBMC research sample at C1D8 may be collected
y = Patients on Arm A who are (1) clinically stable (as per the investigator) following 11 full cycles of treatment and (2) are no longer receiving nivolumab may go twelve weeks (ie three cycles) between clinical assessments and disease assessment imaging. For these patients, three cycles of niraparib may be dispensed at one time. However, all safety blood work must still be collected at D1 (+/- 3 days) of each cycle and will be reviewed by the research team.

7.2 Schedule of Assessments- ARM B (Niraparib + Ipilimumab)

All procedures and assessments are to be completed within ±3 days of the scheduled time point

Table 13. Schedule of Assessments – Arm B

Procedure[a]	Day -28 to Day -1 (unless otherwise specified)	C1D1[b]	C2D1	C3D1	C4D1	C5D1 and onward[y]	EOT	30 Day FU	90 Day FU	LTFU
Informed Consent	X									
Randomization	X									
Demographics/ Medical History[c]	X									
Physical Exam, Height[d], weight	X	x	x	x	x	x	X			
ECOG PS	X	x	x	x	x	x	X			
Vital Signs[e]	X	x	x	x	x	x	X			
Blood Pressure and heart rate monitoring[w]		x	x	x	x	x				
Adverse Events[f]	X	x	x	x	x	x	X	x	x	
Prior/Concomitant Medications and Procedures	X	x	x	x	x	x	X			
Hematology[g]	x[h]	x	x	x	x	x	X			
Serum Chemistry[i]	x[h]	x	x	x	x	x	X			
Lipase	X	x	x	x	x	x	X			
Magnesium	X	x	x	x	x	x	X			
Phosphorus	X	x	x	x	x	x	X			
TSH (Thyroid Function)[j]	X	x	x	x	x	x	X			
HIV AB	X									
CA 19-9 and/or CEA[t]		x	x	x	x		X			

Procedure[a]	Day -28 to Day -1 (unless otherwise specified)	C1D1[b]	C2D1	C3D1	C4D1	C5D1 and onward[y]	EOT	30 Day FU	90 Day FU	LTFU
Serum Pregnancy Test (WOCBP only)[k]	X	x	x	x	x	x	X			
Disease Assessment/ Tumor Scans[l]	X			X[m]		x[m]	X[n]	x[o]		
Archival Tissue (If available[p])	X									
Tumor Tissue Biopsy (if safe/feasible)	X[q]		x[r]							
PBMC/Serum		x[x]			x[v]	x[v]	x[v]			
Blood for WeS		x								
Blood for CTM		x[v]			x[v]	x[v]	X[v]			
Niraparib Dispensation, Administration, Accountability		x	x	x	x	x	X			
Ipilimumab Infusion		x	x	x	x					
Survival Status										X[s]
Follow-Up for MDS/AML										X[s]
Bone Marrow aspirate and biopsy sample[u]		X[u]								

ALP = alkaline phosphatase, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, BUN = blood urea nitrogen, CR = complete response, CT = computed tomography, hrs = hours, MRI = magnetic resonance imaging, PET = positron emission tomography, PK = pharmacokinetics, PR = partial response, SAE = serious adverse event, WBC = white blood cell, WOCBP = women of childbearing potential

a = Treatment cycles are 21 days. Unless otherwise specified, all assessments are to be completed within ±3 days of scheduled time point. Delay of treatment schedule up to 10 days, as allowed by the protocol, is permitted at the discretion of the treating Investigator with approval of the PI (e.g. toxicity, weather, vacation).

b = Any procedures required on Day 1 of Cycle 1 may be omitted if completed ≤3 days earlier during the screening period.

c = Patient's medical record must include prior treatments received, date of progression, and radiology and/or medical report(s) to support assessment of disease progression, and, if applicable, intolerable toxicity to chemotherapy.

d = Height at screening only

e = Vital signs (blood pressure, pulse, and temperature) to be taken pre-dose on clinic visit days. Blood pressure and heart rate should be monitored at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with niraparib.

f = AEs are recorded from the time of signing informed consent through 30 days after last dose of niraparib. Ongoing SAEs will be followed to resolution or until SAE stabilizes.
g = Includes hemoglobin, hematocrit, WBC and differential (with ANC) and platelet count. Blood will be analyzed by a local laboratory. **Weekly CBCs should be performed during the first four weeks of therapy.**
h = to be performed ≤7 days prior to the first dose of therapy or prior to dosing on day 1 to confirm eligibility
i = includes total protein, albumin, creatinine or estimated GFR using Cockgroft Gault formula, BUN, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, CO2, calcium, phosphorous, magnesium and lipase. Blood will be analyzed by a local laboratory.
j = If TSH is abnormal, fT4 and T3 will be drawn. The patient will be clinically managed for thyroid abnormalities at the discretion of the investigator.
k = Women of childbearing potential must have a negative serum pregnancy test result within 24 hours prior to the first dose of niraparib. A serum or urine pregnancy test (investigator's discretion) must be performed ≤3 days prior to Day 1 of every cycle during the treatment phase. A serum pregnancy test must be performed at the End of Treatment visit.
l = Disease assessment to include clinical examination, and appropriate imaging techniques, including CT scans of the chest, abdomen and pelvis, with appropriate slice thickness per RECIST; other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. The same method used to detect lesions at baseline is to be used to follow the same lesions throughout the clinical study if possible. If a patient has known brain metastases, this disease should be evaluated at each required assessment.
m = Tumor scans to be performed within 7 days prior to start of every 3rd cycle or approximately every 9 weeks. Please refer to footnote "y" for procedures for stable patients who are stable following 17 cycles of treatment
n = End of treatment CT scans should be performed if treatment was discontinued for reason other than radiologic disease progression and if previous tumor assessment scan was performed ≥8 weeks prior to EOT visit.
o = If CT scans were not performed at End of Treatment or within 28 days prior to End of Treatment, a CT scan should be performed at the 28-day follow-up visit.
p = Archival tumor tissue, if available, will be collected and stored. (Note: This sample is not required to be submitted on Cycle 1, Day 1, but should be submitted as soon as possible after a patient begins treatment).
q = A screening core tumor biopsy will be collected prior to C1D1 if deemed safe and feasible for those patients who pass the screening evaluation.
r = A core tumor biopsy will be performed during treatment at cycle 2 day 1 if deemed safe and feasible +/- 7 days
s = All patients discontinued from treatment, regardless of reason, should be followed annually until death, loss to follow-up, withdrawal of consent from study, five years, or closure of the study. Follow-up can be performed via telephone, email and/or office visit.
t = Whichever is appropriate for the patient. Patients with a prior history of both markers being elevated will have both drawn serially as per the study calendar.
u = For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria) and other sample testing results related to MDS/AML.
v = Blood samples for PBMC, Serum, and CTM will be collected according to the site lab manual at Cycle 1 and every 3 Cycles (every 9 weeks) thereafter, and at EOT. For patients coming in every 12 weeks, PBMD, Serum and CTM will be collected at that visit.
w= blood pressure and heart rate should be monitored weekly for first 2 months, monthly for first year, and periodically thereafter
x= PBMC research sample at C1D8 may be collected
y = Patients on Arm B who are stable (as per the investigator) following 17 full cycles of treatment may go twelve weeks (ie four cycles) between clinical assessments and disease assessment imaging. For these patients, four cycles of niraparib may be dispensed at one time. However, all safety blood work must still be collected at D1 (+/- 3 days) of each cycle and will be reviewed by the research team.

7.3 Screening Phase

Following written informed consent, and unless otherwise specified, the following assessments will be performed during the 28-day period prior to the first dose of therapy. Assessments performed within this window, but prior to patient signing informed consent, are acceptable only if confirmed to have been standard of care.

- Demographic information (birth date, race, gender, etc.), including smoking status.
- Medical/oncology history, including date of cancer diagnosis, prior treatments and any surgical procedures
- Physical examination of body system, height and weight
- ECOG performance status (16.1 Appendix A)
- Vital signs (blood pressure, pulse, and temperature)
- Prior and concomitant medications and any surgical procedure
- Hematology (hemoglobin, hematocrit, WBC and differential [with ANC], and platelet count) ≤7 days prior to first dose of niraparib.
- Serum chemistry (total protein, albumin, creatinine or estimated GFR using Cockcroft Gault formula, BUN, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, CO2, calcium, phosphorous, magnesium and lipase) ≤7 days prior to the first dose of treatment.
- Serum pregnancy test for women of childbearing potential (≤3 days prior to the first dose of therapy)
- HIV antibody
- Tumor assessments should consist of clinical examination, appropriate imaging techniques including CT scans of the chest, abdomen and pelvis, with appropriate slice thickness per RECIST; other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. The same method used to detect lesions at baseline is to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment.
- FFPE archival tumor tissue sample, if available. Refer to the site Laboratory Manual for detailed sample handling instructions. (Note: this sample is not required to be submitted on Cycle 1, Day 1, but should be submitted as soon as possible after a patient begins treatment)
- Tumor tissue core biopsy if considered safe and feasible (patients who pass screening only). Tumor tissue will be processed locally as formalin-fixed paraffin-embedded (FFPE) tissue. Refer to the site Laboratory Manual for detailed sample handling instructions.
- AE monitoring (after signing informed consent)

7.4 Treatment Phase

The following procedures should be completed *before* the first dose of study therapy is administered, unless otherwise indicated.

7.4.1 Day 1 of Cycles 1-4

- Physical Examination
- Weight
- ECOG performance status (16.1 Appendix A)
- Vital signs
  - blood pressure and heart rate should be monitored weekly for first 2 months, monthly for first year, and periodically thereafter
- Concomitant medications and procedures
- Hematology
  - Weekly CBCs should be performed during the first four weeks of therapy
- Serum chemistry including magnesium, phosphate and lipase
- CA 19-9 and/or CEA measurement
- TSH measurement
- Correlative Research Blood samples will be obtained for Serum, PBMC, Whole Exome Sequencing (C1 only), and Circulating tumor material
  - ARM A: Blood samples for PBMC, Serum, and CTM will be collected according to the site lab manual at Cycle 1 and every other Cycle (every 8 weeks) thereafter; one additional PBMC may be drawn on C1D8. For patients coming in every 12 weeks, PBMD, Serum and CTM will be collected at that visit.
  - ARM B Blood samples for PBMC, Serum, and CTM will be collected according to the site lab manual at Cycle 1 and every 2 Cycles (every 9 weeks) thereafter; one additional PBMC may be drawn on C1D8. For patients coming in every 12 weeks, PBMD, Serum and CTM will be collected at that visit.
- Adverse event monitoring
- The treatment core biopsy will be performed +/- 7 days of cycle 2, if considered feasible and safe as by the first reassessment staging scan and evaluation by the clinical investigator and the performing department.
- Study drug accountability (Cycles 2-4)
- Niraparib dispensation
- Nivolumab (Arm A) or Ipilimumab (Arm B) administration

Niraparib will be dispensed to the patient in sufficient quantity to last until Day 1 of the next treatment cycle. Patients will ingest niraparib once daily at about the same times every day. Bedtime dosing may mitigate nausea. Food does not affect the absorption of niraparib, therefore

niraparib may be taken without regard to meals. If a patient vomits or misses a dose of niraparib, an additional dose should not be taken. The next dose should be taken at a regularly scheduled time.

Patients will keep all unused pills and containers (empty, partially used, and/or unopened) for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described the protocol). Patients will record dosing information in their dosing diary.

7.4.2 Day 1 of Cycles 5 and Beyond, Both Arms

Patients will be instructed to refrain from taking their first dose of oral niraparib at home on the day of their clinic visits because certain assessments must be performed prior to dosing.

The following procedures will be completed prior to oral niraparib on Day 1 of Cycles 5 and beyond:

- Physical examination
- Weight
- ECOG performance status (16.1 Appendix A)
- Vital signs
  - blood pressure and heart rate should be monitored monthly for first year, and periodically thereafter
- Concomitant medications and procedures
- Hematology
- Serum chemistry including magnesium, phosphate and lipase
- TSH measurement
- CA 19-9 and/or CEA measurement
- Correlative Research Blood samples will be obtained for Serum, PBMC, and Circulating tumor material
  - ARM A: Blood samples for PBMC, Serum, and CTM will be collected according to the site lab manual at Cycle 1 and every other Cycle (every 8 weeks) thereafter
  - ARM B Blood samples for PBMC, Serum, and CTM will be collected according to the site lab manual at Cycle 1 and every 2 Cycles (every 9 weeks) thereafter
- Disease/ tumor assessment (using the same methodology as was used at screening [e.g., CT scan]) prior to the start of every 2 cycles (Arm A) or every 3 cycles (Arm B) (within 7 days before is permitted) relative to start of treatment on Day 1 of Cycle 1 through to 18 months on study, then every 16 calendar weeks (within 5 days before is permitted) relative to the start of treatment on Day 1 of Cycle 1. Timing of disease/tumor assessments is relative to Day 1 of Cycle 1 after enrollment. Blood sample for circulating tumor material
- AE monitoring

- Study drug accountability
- Niraparib dispensation
- Nivolumab administration (Arm A only)

Niraparib will be dispensed to the patient in sufficient quantity to last until Day 1 of the next treatment cycle. Patients will ingest niraparib once daily at about the same times every day. Bedtime dosing may mitigate nausea. Food does not affect the absorption of niraparib, therefore niraparib may be taken without regard to meals. If a patient vomits or misses a dose of niraparib, an additional dose should not be taken. The next dose should be taken at a regularly scheduled time.

Patients will keep all unused niraparib and containers (empty, partially used, and/or unopened) for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described the protocol). Patients will record dosing information in their dosing diary.

7.4.3 Tumor Assessments

Tumor assessments will be performed every 2nd cycles or every 8 weeks (+/- 7 days) for Arm A and every 3rd cycle, or every 9 weeks (+/- 7 days) for Arm B, always prior to the first day of the next cycle of therapy.

7.4.4 End of Treatment Visit

The following procedures will be performed for all patients as soon as possible after the last dose of study therapy:

- Physical examination
- Weight
- ECOG performance status (Appendix A)
- Vital signs
- Concomitant medications and procedures
- Hematology
- Serum chemistry
- Magnesium, phosphate and lipase
- TSH measurement
- CA 19-9 and/or CEA measurement
- Serum or urine pregnancy test
- Correlative Research Blood samples will be obtained for Serum, PBMC, and Circulating tumor material

- Tumor assessment scans if patient discontinued therapy for reasons other than radiologic disease progression and if previous tumor assessment scan was performed ≥8 weeks prior to EOT visit.
- AE monitoring
- Study drug accountability

7.5 30-day Follow-up Visit

The following procedures will be performed for all patients at 30 (±3) days after the last dose of study therapy. At least 2 documented attempts will be performed by study team to contact the subject.

- AE monitoring (ongoing SAEs should be followed until resolution or stabilization)
- If tumor assessment scans were not performed at End of Treatment or within 30 days prior to End of Treatment, a CT scan should be performed at the 30-day follow-up visit.

7.6 90 or 100 Day Follow-up Visit for MDS/AML

All patients will have intermittent monitoring for MDS/AML for up to 5 years as described in long-term follow up Section 7.7. Patients who received nivolumab (Arm A) will have an additional follow-up visit at 100 days (±14) days after the last dose of study therapy. Patients who received ipilimumab (Arm B) will have an additional follow-up visit at 90 days (±14) days after the last dose of study therapy. At least 2 documented attempts will be performed by study team to contact the subject.

- AE monitoring (ongoing SAEs should be followed until resolution or stabilization)
- MDS and AML are Adverse Events of Special Interest (Section 10.1.4) and should be reported to the PI and sponsor. Follow-up for MDS/AML can be performed via the telephone. If subject reports a diagnosis of MDS/AML and if feasible at least 2 documented attempts will be made to obtain appropriate documentation (i.e., laboratory and/or pathology reports).

7.7 Long-term Follow-Up

All subjects will be followed annually for survival and MDS and/or AML until death, loss to follow-up, withdrawal of consent from study or for 5 years, whichever occurs first.

- For Overall survival information and MDS/AML follow-up can be performed via telephone, email or, Electronic Medical Record (EMR) review. At least 2 documented attempts will be performed by study team to contact the subject. If attempts to contact are unsuccessful the subject will be considered lost to follow up. Death Records and SSDI will still be used for survival purposes.

7.8 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules or AEs. The Investigator or the Sponsor (if applicable) may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects who withdraw early will have one final visit to collect investigational product and to follow up regarding adverse events.

7.8.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw consent to participate in the study will be seen for one final visit to collect the investigational product. During this visit they will be asked for permission to have the study team look into their survival status via publicly available means.

8 STUDY EVALUATIONS AND MEASUREMENTS

8.1 Medical Record Review

The following information will be extracted from the medical record of each subject prior to the first dose of study therapy.

- Past medical/oncologic history including date of diagnosis, prior treatments, date of progression, and radiology and/or medical report(s) to support assessment of disease progression, and, if applicable, intolerable toxicity to chemotherapy.
- Detailed family history of all cancers
- Any previously performed genetic testing or sequencing (of tumor tissue, circulating tumor DNA and/or germline)

8.2 Physical Examination

Physical examination will include all of the major body systems. Physical examinations will be performed at screening (complete) and at most study visits (limited as appropriate).

8.3 Body Weight and Height

Height will be measured during the Screening visit only. Weight will be measured per institutional guidelines.

8.4 Vital Signs

Vital signs will include blood pressure, pulse and body temperature. Vital signs will be performed at most study visits.

8.5 ECOG Performance Status

ECOG performance status (16.1 Appendix A) will be assessed at Screening, on Day 1 of each cycle, and at the End of Treatment visit. ECOG performance status should be assessed by the

same study personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

8.6 Clinical Laboratory Evaluations

Certified local laboratories will perform study-related clinical laboratory tests according to institutional procedures, and the results will be reviewed by the investigator. The panels of laboratory tests to be performed are shown below:

Hematology: Hemoglobin, hematocrit, WBC and differential (with ANC), sample collection (whole blood) for cytogenetic analysis, and platelet count at Screening, during treatment, and at the End of Treatment visit. Screening hematology results must be reviewed by the investigator prior to the start of treatment with study treatment. During the treatment phase, results must be evaluated by the investigator and acted upon, as appropriate, within 24 hrs. of receipt.

Clinical Chemistry: Total protein, albumin, creatinine or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, TSH, glucose, sodium, potassium, chloride, CO2, calcium, and phosphorus at Screening, during treatment, and at the End of Treatment visit.

Tumor Markers: CA 19-9 and/or CEA (whichever is appropriate for the patient) will be measured on day 1 of each cycle and at the End of Treatment visit.

Serum/Urine Pregnancy: For women of childbearing potential only. Serum pregnancy test is to be performed within 24 hours prior to first dose of niraparib, nivolumab or ipilimumab and at the End of Treatment visit. Serum or urine pregnancy test (per investigator's discretion) is to be performed ≤3 days prior to the start of every cycle during the treatment phase.

Laboratory reports will be reviewed by the investigator or sub-investigator who will then comment on out-of-range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results, as well as results of any additional tests performed as follow-up to the abnormalities, will be documented on the eCRF as an AE. Refer to Section 10.4 for guidelines on reporting of abnormal laboratory values as AEs.

8.7 Efficacy Evaluations

8.7.1 Tumor Assessments

Tumor assessments will be performed at Screening and within 7 days prior to the start of, of every 2nd cycle (Arm A) or every 3rd cycle (Arm B) and at the End of Treatment visit. If a CT scan was not performed at the End of Treatment visit, a CT scan should be performed at the 28-day Follow-up visit. Tumor response will be interpreted using RECIST Version 1.1 (16.2 Appendix B).

Tumor assessments should consist of clinical examination and appropriate imaging techniques (CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. If a patient has known brain metastases, this disease should be evaluated at each required assessment. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout

the clinical study. Investigators should perform scans of the anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status.

8.7.2 Tumor Markers

CA 19-9 and/or CEA (whichever is appropriate for the patient) will be collected on Day 1 of every cycle and at the End of Treatment visit.

8.8 Genetic Testing and Correlative Science

All enrolled patients will undergo whole exome sequencing (WES) of their tumor tissue and blood once they are enrolled in the trial, though results do not impact treatment decision or enrollment. Allele specific loss of heterozygosity will also be assessed in those with an identified HRD, as described below.

Allele specific copy number states were determined using Sequenza and used to calculate the HRD scores non-telomeric allelic imbalance (NtAI)[17], large state transitions (LST)[18], and genomic LOH (HRD-LOH)[19] using custom R-scripts, which are available upon request. Non-telomeric allelic imbalance (NtAI) scores were derived from the Sequenza data by summing the number of segments of allelic imbalance that were post-centromeric to the sub-telomeric regions and >11Mb in length. Large state transition (LST) scores were derived from the Sequenza data by summing the number of breakpoints creating >3Mb segments that were >10Mb from one another. Raw LST scores were corrected for ploidy (LSTm) using the equation LSTm = LST – 15.5 x ploidy. Genomic loss of heterozygosity (HRD-LOH) scores were derived from Sequenza data by summing the number of segments of LOH >15Mb in length excluding segments found on Chromosome 17. HRD-scores were calculated blinded to locus-specific LOH status.

Our specific choice of sequencing tests will be determined by available resources and technology. The Nathanson Laboratory will perform this sequencing.

Copies of any previously performed sequencing results (tissue, circulating tumor DNA or germline) will be collected.

Results of testing performed for whole exome sequencing in Dr. Nathanson's lab will be neither included in the medical record nor shared with the subject. Results may prompt additional testing that would be conducted in a CLIA certified lab.

8.9 Immune Endpoints

8.9.1 Specimen Collection

Tumor tissue (fresh or if not available, archival) must be available or collected prior to the start of treatment. A second treatment biopsy will also be obtained prior to C2D1, if considered safe and feasible. Blood for plasma and peripheral blood mononuclear cells (PBMC) will be collected at baseline and serially during therapy as noted above. Tumor samples and blood samples will be processed according to the study Laboratory Manual in the Vonderheide Laboratory (Human Immunology Core – HIC).

8.9.2 Immune Correlative Science

Analysis of Myeloid and B cell Activation: Using un-manipulated peripheral blood, monocytes, B cells, dendritic cells before and after treatment can be analyzed using flow

cytometry to measure cell surface immune markers using a panel of immune parameters such as CD11b, CD19, CD123, CD11c (to define the subsets) and CD86, MHC class I and II, CD70, and CD54 (to measure activation). For each parameter and each cell type, the percentage of cells positive for the marker and/or MFI at time points after treated can be compared to baseline and the change are calculated as $\%_{after}/\%_{baseline}$ or $MFI_{after}/MFI_{baseline}$.

8.9.3 Immune Biomarkers

Depending on sample availability, a battery of immune assays is planned, including but not necessarily limited to the following:

Tissue Assessment: Tissue can be analyzed by hematoxylin and eosin staining and by IHC for PD-L1 and for immune markers (such as CD45, CD68, CD3, CD8, CD4, Foxp3, CD20, myeloperoxidase), tumor markers (Ki-67, cleaved caspase 3), vascular (CD31) and stromal markers (collagen type I); and by Masson's trichrome. The tumor may also be assessed by a mutational panel and if sufficient material is available, tumor whole exome sequencing (WES) and RNA sequencing may be performed. If RNA quality is insufficient, Nanostring technology or equivalent for immune activation gene expression may be performed instead of RNAseq or in addition. From germline WES from PBMC, HLA type can be determined. From tumor WES, tumor RNA-Seq, and germline WES, patient specific neo epitopes arising from tumor somatic missense mutations can be predicted bio-informatically.

Analysis of T-cell activation: Together with complete blood count differentials, multiplex flow cytometry analysis of PBMC can be used to measure both the percentages and absolute count (cells/mm^3) of important T cell subsets defined by immunophenotyping, such as total CD3+ cells, CD3+ CD8+ T cells, CD3+ CD4+ T cells, and CD3+ CD4+ Foxp3+ regulatory T cells. For each subset, differentiation status (e.g., naïve, central memory, effector memory) or activation vs. exhaustion status can be assessed using additional markers such as Eomes, Tbet, Granzyme B, Ki-67, CD45RA, ICOS, CD45RO, CCR7, CD28, CD27, CD57, CD25, CD69, HLA-DR, CTLA4, and PD-1. When possible, trends will be tracked in T cell subsets based on analysis of multiple post-treatment samples. NK cells subsets will also be assessed using CD16 and CD56, with CD69 as an activation marker.

An analysis of PBMC may be additionally performed using CyTof technology for deeper analysis of immune subsets and activation status in peripheral blood.

Immune activation may be additionally assessed using RNAseq of PBMC.

Inflammatory Cytokines/Chemokines: Plasma will be used to determine concentrations of cytokines including TGF-β, IL-1, TNF-α, IL-6 and others using a multiplex platform.

TCR Deep Sequencing: DNA isolated from PBMC (as well as from paraffin embedded tissue) can be analyzed by deep sequencing to detect and track specific TCR clones. This technique permits assessment of specific adaptive immune response independent of having to know the particular relevant tumor antigen, which of course may vary patient to patient. Comparison of TCR beta sequence data in serial samples from blood and tumor can demonstrate de novo evolution of an anti-tumor T cell repertoire.

Circulating tumor material: Plasma samples may be tested for circulating biomarkers including cell free DNA and tumor cells. Testing will be performed at the Carpenter Laboratory, University of Pennsylvania.

Additional research: Beyond the assays noted above, and provided that sample material is left over, and with approval of the overall PI and sponsor, investigators may perform additional research assays on tumor or blood samples collected in this protocol.

9 STATISTICAL PLAN

This is a two-arm Phase Ib/II study to evaluate safety and progression-free survival in 84 eligible patients. Enrollment is expected to continue for 36 months and follow-up will continue for 6 additional months, prior to the final analysis of PFS. The null hypothesis is that the PFS rate at 6 months (PFS6 rate) is 44% (same as reported for standard therapies) and the alternative hypothesis is that the PFS6 rate has been increased to 60%.

9.1 Primary Endpoints

Safety and progression-free survival at 6 months are primary endpoints. Safety will be assessed in 6 patients. If 1 or fewer DLTs are observed in 6 patients, then the current Niraparib dose will be declared the MTD. Progression-free survival defined as the time from start of experimental therapy to the occurrence of disease progression according to RECIST v1.1, as assessed by the investigator, or death from any cause. Patients who are alive and progression-free will be censored on the most recent date that documents progression-free status (i.e., scan date or clinic visit date). The PFS6 rate and 95% confidence interval will be estimated from the Kaplan-Meier curve.

9.2 Secondary Endpoints

The secondary endpoints are:

1. The incidence of adverse events (AEs), clinical laboratory abnormalities and dose modifications.
2. Identification of HRDs in patients who have achieved stability on platinum-based therapy via whole exome sequencing of tissue and blood (germline).
3. Correlation of HRDs with response to treatment with niraparib plus immune checkpoint blockade therapy.
4. Correlation of immune activation prior to and during therapy with response to treatment with niraparib and immune checkpoint blockade therapy.
5. Objective response will be scored per RECIST v.1.1 as assessed by radiology review.
6. Objective response rate (ORR) is defined as the proportion of patients who achieve a complete or partial response, as determined by RECIST.
7. Duration of response (DOR) is defined as the time from first documentation of complete or partial response by RECIST v.1.1 to date of disease progression or death due to any cause. Responders who have not progressed will be censored on the most recent date that documents progression-free status.
8. Overall survival (OS) is defined as the time from start of study therapy to death due to any cause. Patients who are alive will be censored on the most recent date of patient contact.

9.3 Sample Size and Power Determination

9.3.1 Statistical Methods

We plan to enroll 84 patients in a two-arm phase Ib/II design. Patients will be randomized in a 1:1 allocation to either Niraparib + Ipilimumab or Niraparib + Nivolumab. First, safety will be assessed in the first 6 patients on each arm. If 1 or fewer of 6 patients have DLT, then the current dose of Niraparib will be declared the MTD. Otherwise, the dose of Niraparib will be de-escalated and 6 more patients will be treated. Progression-free survival rate at 6 months (PFS6) will be the other primary clinical outcome and it will be estimated using the Kaplan-Meier method. Based on prior research [1, 2, 20, 21] the null hypothesis is that the PFS6 rate in this population of subjects is 44%. The alternative hypothesis is that the PFS6 rate is 60%. Forty-two patients per arm, expected to give 30 events, (this number includes the first 6 patients upon which safety was established) provide 81% power per arm for a log rank test, to detect this increase in PFS6, at a two-sided 5% significance level, assuming an exponential distribution and that enrollment will continue for 36 months with an additional 6 months of follow-up prior to the final statistical analysis. Secondary outcomes include overall survival (OS) and objective response rate (ORR); median OS and 95% confidence interval will be estimated by the Kaplan-Meier method and ORR will be an estimated percentage with 95% confidence interval. Toxicities will be graded and tabulated and Grade 3 or higher toxicity rates will be calculated. With 42 patients per arm, we have 88% power to detect any toxicity occurring at a rate of 5% or more.

Translational Statistics: Genomic and immune endpoints will also be assessed. Serial testing of the presence of mutations using tissue and peripheral blood will be described using graphical plots and descriptive statistics.

9.3.2 Baseline Data

All demographic and baseline characteristics will be summarized for the safety population.

The following variables will be summarized with frequent tabulations:

- Time since diagnosis (months)
- Baseline laboratory parameters: graded based on NCI CTCAE version 5.0

Descriptive statistics may also be used to summarize these variables.

9.3.3 Efficacy Analysis

All efficacy evaluations will be conducted using the efficacy population (Section 9.4). If the lower bound of the 95% confidence interval for PFS6 is > 44% (the null hypothesis value) then the study will be declared a success.

9.3.4 Safety Analysis

All safety evaluations will be conducted using the safety population (Section 9.4).

9.4 Subject Population(s) for Analysis

The following analysis populations are defined for the study:

Safety Population: The safety population will consist of all patients who received at least one dose of study treatment.

Efficacy Population: The efficacy population will consist of all patients who received at least one dose of study treatment and had a least one post-treatment assessment of response by RECIST v.1.1 (16.1 Appendix A). Patients who do not have at least one post-treatment assessment of response will be replaced.

10 SAFETY AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Unanticipated Problems Involving Risk to Subjects or others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

10.1.2 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests is considered by the investigator to be of clinical significance

10.1.3 Serious Adverse Event

Any untoward medical occurrence that, at any dose;

- Results in death;
- Is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization* or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event**

*Exception: Preplanned (at time of informed consent) hospitalization for elective procedures, for protocol compliance or social reasons, or for observation will not be considered criteria for an SAE. The reason for the planned hospitalization should be documented. Complications experienced during these hospitalizations must be reported as SAEs if hospitalization is prolonged due to AE, or if the complication meets other serious criteria).

**Medical and scientific judgment should be exercised in determining whether situations or events should be considered serious adverse events: an important medical event may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the study drug.

Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as a SAE with CTC Grade 5 (fatal outcome) indicated.

10.1.4 Adverse Events of Special Interest (AESIs) for Niraparib

An Adverse Event of Special Interest is defined as any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment.

Adverse Events of Special Interest (AESI) for niraparib include the following:

- Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)
- Secondary cancers (new malignancies [other than MDS or AML])
- Embryo-fetal toxicity

AESIs should be reported on SAE/ MedWatch Report Forms whether serious or not and reported to the Sponsor in 24 hours

10.2 Recording of Adverse Events

At each contact with the patient, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis. All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

AEs that meet the criteria of serious, related to study intervention, and unexpected for the study intervention, qualify for expedited reporting to the Sponsor and regulatory authorities. The Site Investigator will assess all SAEs occurring at his/her site and evaluate for "unexpectedness" and relationship to study drug. The Site Investigator is required to complete a Report for the events identified as serious, study drug related and unexpected, using the SAE/Medwatch Form.

A copy of this report should be kept at the site.

10.3 Intensity of Adverse Events

The severity of each AE will be graded using the NCI CTCAE, Version 5.0 grading scale

For AEs not covered by NCI CTCAE, the severity will be characterized as mild, moderate, severe, or life-threatening according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe events interrupt the patient's usual daily activities and hospitalization (or prolongation of hospitalization) may be required
- Life-threatening events require urgent intervention to prevent death

10.4 Causal Relationship of Adverse Events to Study Drugs

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, de-challenge or re-challenge with the study drugs.

Table 14. Causal Relationship of Adverse Events to Study Drugs

Not Related To Study Drugs	• An AE that is clearly due to extraneous causes (e.g., concurrent disease, concomitant medications, disease under study, etc.) • It does not follow a reasonable temporal sequence from administration of the study drug. • It does not follow a known pattern of response to study drug • It does not reappear or worsen when study drug is restarted. • An alternative explanation is likely, but not clearly identifiable.
Possibly, Probably or Definitely Related to Study Drugs	• An AE that is difficult to assign to alternative causes. • It follows a strong or reasonable temporal sequence from administration of study drug. • It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. • It follows a known response pattern to study drug • It is confirmed with a positive re-challenge or supporting laboratory data.

Causality and expectancy of the adverse events will be assessed for the individual drugs and the combination.

10.5 Outcome and Action Taken

The investigator will record the action taken and outcome for each AE according to the following criteria:

Action Taken with Study Drug (note all that apply)

- None
- Dose reduced/delayed
- Study drug temporarily interrupted
- Study drug permanently discontinued
- Other (specify)

Outcome

- Recovered
- Recovered with sequelae
- Recovering/ Resolving/ Improving
- Ongoing
- Death
- Lost to follow-up

10.6 Adverse Event Reporting Period

The study period during which AEs must be reported is defined as the period from the initiation of consent through 100 days (nivolumab patients) or 90 days (all patients) after patient End of Treatment Visit.

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical and good clinical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized through 100 days (nivolumab patients) or 90 days (ipilimumab patients) after the last dose of study drug. Any SAEs, AESIs, and treatment related Grade 3/4 AEs must be followed until resolution or stabilization, or until lost to follow-up.

10.7 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period

10.8 General Physical Examination Finding

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

10.9 Post-Study Adverse Event

All unresolved AEs should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or AE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

10.10 Abnormal Laboratory Values

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant

10.11 Pregnancy or Drug Exposure

If a patient becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring in a study patient during study participation or within 6 months of last dosing, or pregnancy occurring in a partner of a study patient during study participation or within 90 days of last dosing must be reported to the Penn Sponsor within 1 business day on a MedWatch Form. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions, but should be reported to the Sponsor Institution. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome (e.g., maternal serious complications, spontaneous abortions therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, and birth defect).

A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, an updated MedWatch form should be completed and reported to the UPenn Sponsor.

AEs, SAEs, or AESIs that occur during pregnancy will be assessed and processed according to the AE or SAE/AESI processes using the appropriate MedWatch report form.

10.12 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.13 Reporting to the UPenn Sponsor

10.13.1 Adverse Events

The study clinician will immediately report (1 business day) to the sponsor any serious adverse events, whether or not considered related to one of the three investigational products, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that one of the three investigational caused the event.

The study clinician will immediately report Adverse Events of Special Interest to the sponsor.

Investigators and the protocol sponsor must conform to the AE reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum, those events that must be reported are those that are:

- Related to study participation,
- Unexpected, and
- Serious or involve risks to subjects or others

If the AE is considered serious, the investigator should report this event to the sponsor within one (1) business day. The IRB should be notified as per institutional guidelines. The sponsor medical director and site IRB, as appropriate, will make an immediate determination about the necessity to modify the protocol, include additional information in the consent form, inform previous participants, temporarily hold enrollment of patients, or terminate the study. The study will proceed only if the medical director and site IRB all agree on this course of action.

The investigator or qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF. The event, including the investigator-determined causality to study drug should be reported via SAE/MedWatch (link below) to the Medical Monitor.

For reporting information, please refer to the Manual of Procedures.

Events significant enough to necessitate modification of study drug dosing will be captured on an appropriate eCRF module (“Study Drug Dosing” page).

New information regarding the SAE shall be reported as it becomes available and in the same manner that the initial SAE (MedWatch form). All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

10.13.2 Reporting Product Quality Complaints for Niraparib

Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the investigator or qualified designee to the UPenn Sponsor. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is

required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

10.14 Investigator Reporting: Local Reporting Requirements

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

10.15 Protocol Exceptions

A one time, intentional action (planned prospectively) or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. Advance documented IRB and DSMC approval is required.

For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the DSMC.

The following information must be contained in your exception request:

- When it is needed and why it is needed in that timeframe
- Has the Medical Monitor or Sponsor approved and provide the documentation of approval
- Is this an exception from eligibility, treatment, disease progression, study calendar windows, etc.
- Why the exception is needed (cite the section(s) of the protocol) along with the full clinical details of the subject. This must be determined by the sub-Investigator or PI.
- The reason why the protocol currently doesn't allow the situation for which an exception is being requested. This must be determined by the sub-Investigator or PI.
- If there are plans to amend the protocol and if not, why not.

If additional follow-up or interventions will be required in order to protect the subject as a result of this exception.

Exceptions to eligibility, treatment/dosing, contraindicated treatment/therapies/interventions or safety tests may be rejected by the Sponsor.

10.16 Protocol Deviations

Any unintentional action or process that departs from IRB approval and is identified retrospectively. The deviation is reportable to the DSMC and the IRB within 10 days from the time the event becomes known to the study team only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, or the event has the potential to qualify as serious or continuing noncompliance.

If the PI determines that a deviation has any potential to impact participant safety (harm and/or risk), or the integrity of data produced from the participant, or some other overall impact on the

study, the PI must report the deviation to the IRB and DSMC as described above. The IRB will make the final assessment of the impact. The DSMC will assess for additional safety and scientific integrity concerns.

The following information must be contained in your deviation report:

- When it happened? When the study team (any member) became aware
- The full description of the deviation including important dates, test results, actions taken towards the subject, etc. Also, why it happened and how it was identified.
- Was the Medical Monitor or Sponsor notified? If so, their response?
- The PIs assessment of the impact on risk, safety and/or outcome. If no impact, why. If impact, what and what will happen next.
- The corrective actions that have been implemented to date and the impact of those corrective action plans.
- Future corrective action plans (if applicable) and the impact of those plans.
- If there are plans to amend the protocol (if applicable to prevent future deviations) and if not, why not.

If the PI determines that the event had no potential to impact participant safety (harm and/or risk) or the integrity of data produced from the participant, the PI must fully document his/her rationale for each category (risk, harm, and participant data).

10.17 Investigator Reporting to Sponsor of Exceptions and Deviations

The PI is required to report all SAEs, exceptions and deviations to the Sponsor within 1 business day of learning. The Study Sponsor will report to collaborators per contract and the FDA according to 21 CFR 312.

10.18 Medical Monitor

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as adherence to the study protocol. Medical monitoring will include real time reporting (one Business Day) and an assessment annually of the number and type of adverse events to the study medical monitor, Dr. Vivek Narayan. Additionally, the Medical Monitor will be consulted for protocol exceptions and deviations and as needed for enrollment decisions as noted above.

10.19 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.20 Data Collection and Management

This study will use Velos (Penn CTMS) as the data management system. The study case report form (CRF) is the primary data collection instrument for the study and will be electronically created and completed in Velos. CRFs will be provided for each patient. Subjects must not be identified by name on any CRFs. Subjects will be identified by their patient identification number (PID). All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

10.21 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the drug manufacturer. In such an instance, it is the responsibility of the drug manufacturer to inform the investigator/institution as to when these documents no longer need to be retained.

11 STUDY MONITORING, AUDITING, AND INSPECTING

11.1 Study Monitoring Plan

It is the responsibility of the Sponsor to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. This monitoring will include a regular assessment of the number and type of serious adverse events.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the Sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

This study will be monitored in accordance with the specific plan developed for this protocol.

12 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to TESARO and Bristol-Myer Squibb before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

13 STUDY FINANCES

13.1 Funding Source

This clinical study will be supported by funds provided by TESARO and by Bristol-Myers Squibb.

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

14 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

15 REFERENCES

1. Conroy, T., et al., *FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.* N Engl J Med, 2011. **364**(19): p. 1817-25.
2. Von Hoff, D.D., et al., *Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine.* N Engl J Med, 2013. **369**(18): p. 1691-703.
3. Waddell, N., et al., *Whole genomes redefine the mutational landscape of pancreatic cancer.* Nature, 2015. **518**(7540): p. 495-501.
4. Holter, S., et al., *Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma.* J Clin Oncol, 2015. **33**(28): p. 3124-9.
5. Goggins, M., et al., *Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas.* Cancer Res, 1996. **56**(23): p. 5360-4.
6. Carnevale, J. and A. Ashworth, *Assessing the Significance of BRCA1 and BRCA2 Mutations in Pancreatic Cancer.* J Clin Oncol, 2015. **33**(28): p. 3080-1.
7. Cerami, E., et al., *The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data.* Cancer Discov, 2012. **2**(5): p. 401-4.
8. Gao, J., et al., *Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal.* Sci Signal, 2013. **6**(269): p. pl1.
9. Alexandrov, L.B., et al., *Signatures of mutational processes in human cancer.* Nature, 2013. **500**(7463): p. 415-21.
10. Kaufman, B., et al., *Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation.* J Clin Oncol, 2015. **33**(3): p. 244-50.
11. Mateo, J., et al., *DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer.* N Engl J Med, 2015. **373**(18): p. 1697-708.
12. Choi, Y.E., et al., *Platinum and PARP Inhibitor Resistance Due to Overexpression of MicroRNA-622 in BRCA1-Mutant Ovarian Cancer.* Cell Rep, 2016. **14**(3): p. 429-39.
13. Clark, C.E., G.L. Beatty, and R.H. Vonderheide, *Immunosurveillance of pancreatic adenocarcinoma: insights from genetically engineered mouse models of cancer.* Cancer Lett, 2009. **279**(1): p. 1-7.
14. Higuchi, T., et al., *CTLA-4 Blockade Synergizes Therapeutically with PARP Inhibition in BRCA1-Deficient Ovarian Cancer.* Cancer Immunol Res, 2015.
15. *TESARO Summarizes ZEJULA and TSR-042 Data Presented at the 2017 ESMO Annual Meeting*. 2017; Available from: http://ir.tesarobio.com/releasedetail.cfm?releaseid=1039856.
16. Momtaz, P., et al., *Safety of Infusing Ipilimumab Over 30 Minutes.* J Clin Oncol, 2015. **33**(30): p. 3454-8.
17. Birkbak, N.J., et al., *Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents.* Cancer Discov, 2012. **2**(4): p. 366-75.
18. Popova, T., et al., *Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation.* Cancer Res, 2012. **72**(21): p. 5454-62.
19. Abkevich, V., et al., *Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer.* Br J Cancer, 2012. **107**(10): p. 1776-82.
20. Golan, T., et al., *Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers.* Br J Cancer, 2014. **111**(6): p. 1132-8.

21. Heinemann, V., et al., *Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer.* J Clin Oncol, 2006. **24**(24): p. 3946-52.
22. National Cancer Institute. *Common Terminology Criteria for Adverse Events, Version 4.03*. 14 June 2010 [cited 19 November 2014]; Available from: http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
23. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

16 APPENDIX

16.1 Appendix A: ECOG

Table 15. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG Performance Status	
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg light house work or office work).
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable only of limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead.

16.2 Appendix B: Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[23] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm).
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable).
- A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded n millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions:

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

Cystic Lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) because 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 noncystic lesions are present in the same patient, these are preferred as target lesions.

Lesions with Prior Local Treatment:

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions:

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target Lesions:

RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease:

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Table 16. Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10mm
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of all the LD 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 5mm. The appearance of one or more new lesions is also considered progression.

Table 17. Evaluation of Nontarget Lesions

Complete Response	Disappearance of all non-target lesions and normalization of tumor marker levels.
Stable Disease/ Incomplete Response	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one or more lesions and/or unequivocal progression of existing non-target lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered to be a complete responder.

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 PD 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.

Table 18. Evaluation of Best Overall Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

NE = not evaluable

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

Confirmatory Measurement/Duration of Response

Confirmation

CT scans are required at screening and within 7 days prior to the start of every odd numbered cycle (i.e., Cycles 3, 5, 7, etc.). If an initial CR or PR is noted, confirmatory scans must be performed >4 weeks later.

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 PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

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

Duration of Stable Disease

SD 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.

16.3 Appendix C: COVID-19 Study Implication Memo

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

MEMORANDUM

To: Institutional Review Board

cc: Clinical Trials Scientific Review Committee (CTSRMC)
University of Pennsylvania Data and Safety Monitoring Committee (DSMC)
Regulatory Binder (ISF)

From: Kim Reiss Binder, MD

Date: March 16, 2020

Re: UPCC 35217: University of Pennsylvania IRB #: 828516

Regarding: UPCC 35217: PARPVAX: A PHASE IB/2, OPEN LABEL STUDY OF NIRAPARIB PLUS EITHER IPILIMUMAB OR NIVOLUMAB IN PATIENTS WITH ADVANCED PANCREATIC CANCER WHOSE DISEASE HAS NOT PROGRESSED ON PLATINUM-BASED THERAPY

Out of an abundance of caution and in an effort to ensure the safety of our study participants, due to the implications of COVID-19, I have reviewed the protocol for the above noted study and have implemented the following changes as needed on a participant basis to eliminate apparent immediate hazards/harm where necessary.

In submitting this memo, I reference the applicable federal regulation … (a) Follow written procedures for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects. 21 CFR 56.108(a)(4).

This memo will now serve as a protocol clarification letter, noting permissible protocol adaptations to be carried out until further notice as determined necessary on a participant level and as the situation with COVID-19 continues to evolve. A follow up memo will be provided if additional measures are determined to be required and when the below noted alterations are determined to no longer be necessary.

These changes include:

1) **Alterations to the Enrollment Status of the Study:**
This study has been deemed critically important to our patient population for whom comparable standard of care therapeutic options do not exist and patients would be less immunosuppressed on this clinical trial than on chemotherapy. Without a satisfactory alternative, delaying protocol therapy poses a greater risk to subjects than the risks of protocol alterations and coming to the site during the emerging COVID-19 epidemic. At this time, we have reviewed our staffing model and determined there is adequate resources (both research and clinical) to carry out the protocol safely. Unless otherwise directed by the Sponsor, this study remains open to accrual at the University of Pennsylvania.

2) **Alterations to Informed Consent:**
Telemedicine (i.e., HIPAA-compliant virtual visit or telephone-based assessment) may be used to facilitate the informed consent discussions if a face-to-face scenario is not deemed practical or safe. In those cases, a copy of the complete IRB-approved consent document will be sent to the participant (or potential participant) in advance (e.g., email/scan, fax, or postal mail). After the informed consent discussion, the participant will be asked to sign the form and return a copy to the study team in a way that is practical and convenient (e.g., email/scan or fax). The informed consent copy will be signed by the study team member obtaining informed consent and filed in the designated investigator site file location. Part 11 compliant electronic signature is acceptable. This process will be documented in the Electronic Medical Record (EMR).

Page 1 of 2

3) **Alterations to drug supply/administration:**
   a. For patients who require oral medication *only* (niraparib) and who are not receiving ipilimumab or nivolumab infusions, study drug will be shipped to participants who are scheduled to have remote research visits due to refusal; travel restrictions; or other extenuating circumstances, including University of Pennsylvania and UPHS recommendations. All infusions will still be adminstered at the Perelman Center for Advanced Medicine Outpatient Infusion Suite.
   b. The study team will work to ensure participants can continue to receive their oral medications without disruption. This includes temporary allowance to (1) ship oral medications from the site to the participant, and/or (2) extra or early dispensation. As deemed permissible by the Sponsor, the product will be packaged, labeled, and shipped by the Pharmacy of Record per FDA form 1572 direct to-participant . After review of the necessary lab results shipment by UPS or FedEx will be utilized to ensure the drug shipment is tracked, a signature will be required as proof of mail delivery. Because oncology patients represent a population especially vulnerable to COVID-19, we will temporarily accept the signature of a trusted person Upon delivery, the participant will e-mail/call the study team to declare the authorized signature and their relationship to the participant (if applicable) and to describe the package being sure to note any issues such as damaged packaging, evidence of tampering, etc. The participant will be instructed to immediately return a copy of the shipping slip to the study team via e-mail/scan or fax. If the participant is not able to return a copy of the shipping slip, a study team member will print documentation of delivery using the package tracking tool through the vendor services (e.g., FedEx, UPS, etc.) website. The participant will also be provided with verbal instructions to return the shipping slip (if not already returned), bottle along with any unused product at their next in-person visit. This discussion will be documented in the Electronic Medical Record (EMR).
   c. In the event that the package is lost/damaged during shipping, the Sponsor will be notified and product will be re-shipped as soon as possible. Pre-treatment laboratory assessments will be redrawn at my discretion. Other assessments may be repeated on a case-by-case basis.

4) **Alterations to the type of study visits:**
   For participants who will have remote study visits with the physician-investigators and/or staff, this will be done via phone or another HIPAA compliant Telemedicine method used by UPHS. All visits will be documented in the participants' charts and in the EMR.

5) **Alterations to the schedule of study visits/procedures:**
   Due to the nature of this situation, and the necessary steps taken to protect patient health, some research procedures may not be completed, including:

   Research-only activities that do not inform the safety of participants on the study:
   - Study biopsies
   - gDNA blood sample collection
   - ctDNA blood sample collection
   - PBMC blood sample collection
   - Vitals (Every Study Visit)
   - Physical exam, including weight

   For the above listed procedures the following protocol endpoints, and their associated procedures will affect the trial data:
   - ctDNA and PBMC blood sample collection
     - No objectives are impacted
   - Study biopsies and gDNA blood sample collection
     - Secondary objective #1: To assess the proportion of tumors in this cohort (with stability or response to platinum therapy) with homologous recombination deficits (HRD).

Study staff, as documented on the protocol delegation of authority log, have been made aware of the above alterations to the conduct of the protocol and have been offerred the opportunity to ask any questions. Formal documentation of this training can be found in the investigator site file.

Kim Reiss Binder, MD

Kim Reiss Binder, MD Digitally signed by Kim Reiss Binder, MD Date: 2020.03.17 10:28:32 -04'00'

Page 2 of 2