PARPVAX2: A PHASE II STUDY OF MAINTENANCE NIRAPARIB PLUS IPILIMUMAB IN PATIENTS WITH METASTATIC PANCREATIC CANCER WHOSE DISEASE HAS NOT PROGRESSED ON PLATINUM-BASED THERAPY

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1 STUDY SUMMARY

Title	PARPVAX2: A PHASE II STUDY OF MAINTENANCE NIRAPARIB PLUS IPILIMUMAB IN PATIENTS WITH METASTATIC PANCREATIC CANCER WHOSE DISEASE HAS NOT PROGRESSED ON PLATINUM-BASED THERAPY
Short Title	Maintenance Niraparib Plus Ipilimumab in Patients with Metastatic Pancreatic Adenocarcinoma Whose Disease Has Not Progressed on Platinum-Based Chemotherapy
UPENN IRB Number	857488
Protocol Number	UPCC 19224
Phase	Clinical Phase II
Methodology	Randomized, Two Arm, Non-Comparative, Open Label
Study Duration	26 months
Study Centers	Abramson Cancer Center at University of Pennsylvania and Dana Farber Cancer Institute

Objectives

Primary:

- To estimate the progression free survival (PFS) of maintenance niraparib/ipilimumab in a population of patients with metastatic pancreatic cancer who have not progressed following 4-6 months of palliative FOLFIRINOX

Secondary:

- To estimate the overall response rate in the experimental arm
- To estimate the disease control rate in the experimental arm
- To estimate the median overall survival in the experimental arm
- To estimate the PFS, ORR, DCR and OS of a non-comparative control arm of patients receiving maintenance chemotherapy
- To evaluate the safety of niraparib plus ipilimumab in the experimental arm
- To determine biomarkers of response, mechanisms of action and immune pharmacodynamics of niraparib/ipilimumab in a population of patients with metastatic pancreatic cancer

Number of Subjects

68 (51 receiving nira/ipi; 17 receiving maintenance FOLFIRI)

Main Inclusion and Exclusion Criteria

KEY INCLUSIONS:

1. Histologically or cytologically confirmed diagnosis of metastatic pancreatic adenocarcinoma
2. Patients must have received first-line FOLFIRINOX chemotherapy for metastatic pancreatic cancer and have received between four and six months of treatment 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.
3. Measurable disease is not required for study entry

   Note: The study will require that at least 80% of enrolled patients (i.e. 55 of all patients) are biopsiable at enrollment. The investigators may require measurable/biopsiable disease as the study progresses in order to achieve this goal.
4. Adequate organ function
5. ECOG performance status of 0-1

KEY EXCLUSIONS:

1. Prior treatment with a PARP inhibitor, ipilimumab, or other inhibitors of cytotoxic T-lymphocyte-associated protein (CTLA-4).
2. Patients who have demonstrated resistance to FOLFIRINOX are not eligible to participate in this study
3. Patients who have a known, pathogenic germline or somatic variant in *BRCA1, BRCA2, PALB2, RAD51C* or *RAD51D* are excluded. Patients with MSI-H or MMR deficient pancreatic cancer are excluded.
4. 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.

5. Received any systemic treatment for pancreatic cancer during the 14 days prior to first dose of treatment.
6. Acute infection requiring intravenous antibiotics, intravenous antiviral or intravenous antifungal agents during the 14 days prior to first dose of study therapy.
7. 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.
8. Has a history of interstitial lung disease or active, non-infectious pneumonitis.
9. 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

This is a two-arm randomized trial of niraparib/ipilimumab vs. a non-comparative control arm designed to test, in the niraparib/ipilimumab arm, study testing the null hypothesis of median PFS (mPFS) of 5 months versus the alternative hypothesis of an mPFS 7.5 months. Assuming exponential survival, with 51 patients enrolled over 14 months and with 12 months of additional follow-up, there is 89% power for the test and 5% 1-sided type I error rate. With 17 control patients, a 90% confidence interval for any binomial parameter (toxicity, response, etc.) would be no wider than 43% percentage points and the chance of observing one or more rare events (4% true probability) is at least 50% and events of true frequency of 9% or higher have at least 80% probability of being observed (1 or more events out of 17 control patients).

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

With the advent of effective multi-agent chemotherapy regimens[1,2] for metastatic pancreatic cancer (mPC)[3], subgroups of patients who show durable responses to treatment are emerging. As a result, a growing population with incurable PC now stay on chemotherapy for many months and even years. These improvements in outcomes are remarkable for a universally lethal illness. However, "perpetual chemotherapy" ultimately fuels therapeutic resistance and drives cumulative toxicities that degrade quality of life. In order to mitigate toxicity, chemotherapy is commonly dose modified in patients who have durable responses, and there are clinical data to support this approach [4,5]. However, non-chemotherapy based maintenance strategies (e.g. PARP inhibitors and immunotherapy) represent an exciting alternative approach due to their favorable toxicity profiles and the possibility of improved outcomes. Taken together, there is an unmet clinical need to identify sustainable, non-chemotherapy based options for patients with mPC who achieve durable stability on first-line palliative treatment.

2.2 Background and Relevant Literature

Maintenance therapy is known to be effective in BRCA and PALB2 mutant patients. Non-chemotherapy based maintenance therapy for PC was first tested in patients with pathogenic variants in *BRCA1, BRCA2,* or *PALB2*: The randomized phase III POLO trial enrolled patients with metastatic, platinum-sensitive PC and pathogenic, germline *BRCA* variants. Chemotherapy was discontinued and patients were treated with maintenance olaparib, a poly-ADP ribose polymerase (PARP) inhibitor vs placebo. Olaparib significantly increased the median progression-free survival (mPFS) compared to placebo[6] and the study led to the FDA approval of olaparib in this setting. We conducted a smaller, single arm, phase II trial of maintenance rucaparib, another PARP inhibitor, in platinum-sensitive patients with advanced PC and germline or somatic *BRCA* or *PALB2* variants, which met the primary endpoint (mPFS 13.1 mo)[7] and led to the addition of maintenance rucaparib in the NCCN guidelines for this broader population. The positive results of these trials are encouraging and behoove us to explore non-chemotherapy based maintenance therapy in a larger, phenotypically selected group of patients, namely: those who do well with front-line FOLFIRINOX.

In a randomized clinical trial, maintenance niraparib plus ipilimumab (nira/ipi) was effective in platinum-sensitive, advanced PC patients. We completed a single-institution, investigator-initiated phase Ib/II trial of maintenance niraparib, another PARP inhibitor, plus either nivolumab or ipilimumab in patients with advanced PC and at least stable disease following ≥4 months of platinum-based chemotherapy[8]. The rationale for combining niraparib with immune checkpoint blockade were based on multiple published *in vivo* models demonstrating that (1) PARP inhibitor activity is dependent on an active immune system and an intact cGAS-STING pathway[9], and (2) there is synergy of PARP inhibitors plus ICB[9,10]. The upregulation of CTLA4 in immunologically "warm" PCs (and the absence of PDL1 upregulation in the same setting), provided additional rationale for exploring ipilimumab in addition to nivolumab[11]. No genomic alteration was required for enrollment on the study. Chemotherapy was stopped, and patients were randomized 1:1 to niraparib plus nivolumab (nira/nivo) (Arm A) or nira/ipi (Arm B). The primary endpoint was PFS, and the primary objective was a PFS6 of 60% in each arm. The study

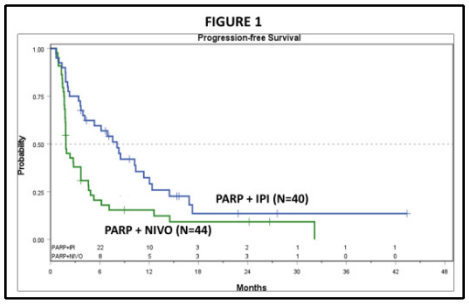


Table 1

	Nira/Nivo	Nira/Ipi
mPFS	1.9mo	8.1mo
PFS6	20.6%	59.6%
PFS12	15.4%	32.3%
ORR	7.7%	15.4%
mOS	13.2mo	17.3mo

enrolled 84 patients (44 Arm A; 40 Arm B). The mPFS of nira/nivo was 1.8 months (PFS6 20.6%) and the mPFS of nira/ipi was 8.1 mo (PFS6 59.6%); the trial was therefore positive in the nira/ipi arm (**Fig 1**). Median overall survival (mOS), overall response rate (ORR), and PFS12, were all numerically higher in the nira/ipi arm, though the study was not powered to assess these endpoints (**Table 1**). Patient demographics and characteristics were similar between the two arms. Additionally, when all patients with known DNA damage repair (DDR) variants were removed from the analysis, the results were unchanged. Given that most patients with a functional DDR deficiency can be successfully identified on routine panel testing[12], the persistent efficacy of the nira/ipi arm after removal of all DDR deficient patients suggests that the results may not be driven by a DNA repair deficiency in this population. We alternatively hypothesize that patients who demonstrated durable responses to chemotherapy may represent an immunologically superior population who, in turn, are able to respond more effectively to the combination of PARP inhibition and anti-CTLA4. *However, the mechanistic basis for response to PARP inhibition and anti-CTLA4 remains unknown.*

Preliminary analysis of immune determinants of treatment response in patients treated with PARP inhibition and immunotherapy. We evaluated the immune composition of our study population. First, we assessed the initial (at cancer diagnosis) and baseline (at study enrollment) neutrophil to lymphocyte ratios (NLRs). Literature suggests that patients with low NLR are more treatment responsive and have improved prognosis compared to those with high NLR[13]. Consistent with this, we identified that our patients had low NLRs at cancer diagnosis, suggesting a superior immune milieu in this population (**Table 2**). Next, we looked for baseline and on-treatment differences in the peripheral blood via evaluation of serially collected peripheral blood mononuclear cells (PBMCs). Patients in the nira/nivo arm had more baseline T-regulatory cells, while patients in the nira/ipi arm had more naïve B cells and proliferating T-cells (**Fig 2**). To explore whether these findings might have influenced response to therapy, we divided patients into progressors (progression in <6mo) and non-progressors (stability for >6mo) and compared the pretreatment levels of naïve B-cells, T-regulatory cells, and double negative T-cells in each group. We found no significant association with levels of these cell types and response to therapy, suggesting alternative determinants of treatment outcomes. *Taken together, we have identified an active maintenance regimen that is, as of yet, is incompletely mechanistically understood.* Therefore, in this proposal we aim to: (1) validate nira/ipi as a maintenance option, (2) explore the pharmacodynamics and mechanisms of this combination and (3) study biomarkers predictive for response to treatment.

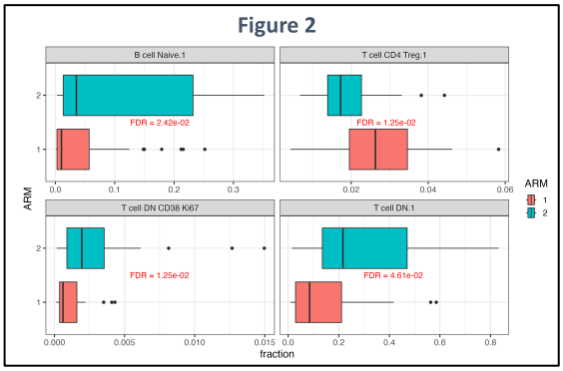


Table 2

Median NLR	At PDAC Diagnosis	At Study Entry
Arm A (Nira/Nivo)	3.4	2.7
Arm B (Nira/Ipi)	2.9	2.8

Our specific aims are:

- Define the activity of maintenance nira/ipi in a population of patients with metastatic pancreatic cancer who have not progressed on first line palliative FOLFIRINOX after 4-6 months of treatment.

- Determine biomarkers of response, mechanisms and immune pharmacodynamics of nira/ipi in a population of patients with metastatic pancreatic cancer.

Clinical impact: We previously demonstrated the efficacy of maintenance niraparib/ipilimumab in a population of patients with advanced pancreatic cancer who had not progressed on platinum-based therapy[8]. We now embark on a second study to validate our results and to provide further insights into the mechanisms of action, pharmacodynamics and biomarkers that predict success or failure of this combination in patients.

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-[8]-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 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.

2.4.1 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 ¾ 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 immune related adverse event (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 Niraparib Plus Ipilimumab

Niraparib has previously been studied in our previously reported phase I/II study[8]. In the phase I portion of the study, the combination of niraparib 200mg PO daily plus ipilimumab 3mg/kg IV Q3 weeks x4 doses was found to be safe. This dosing regimen and schedule was the recommended phase II dose. There was no evidence of toxicity overlap between

the two agents. Most common grade 3 or worse adverse events were fatigue (14%), anemia (11%) and hypertension (9%). There were no treatment-related deaths.

3 STUDY OBJECTIVES

3.1 Primary Objective

- To estimate the progression free survival (PFS) of maintenance niraparib/ipilimumab in a population of patients with metastatic pancreatic cancer who have not progressed following 4-6 months of palliative FOLFIRINOX

3.2 Secondary Objectives

- To estimate the overall response rate in the experimental arm
- To estimate the disease control rate in the experimental arm
- To estimate the median overall survival in the experimental arm
- To estimate the PFS, ORR, DCR and OS of a non-comparative control arm of patients receiving maintenance chemotherapy
- To determine biomarkers of response, mechanisms of action and immune pharmacodynamics of niraparib/ipilimumab in a population of patients with metastatic pancreatic cancer

4 INVESTIGATIONAL PLAN

4.1 General Design

This is a two arm, open-label randomized study of niraparib plus ipilimumab or maintenance FOLFIRI in patients with metastatic pancreatic adenocarcinoma who have achieved disease stability on FOLFIRINOX. The control arm is meant to be non-comparative to the experimental arm and is designed to provide validity to the results.

Patients will be randomized to either Arm A (niraparib + ipilimumab) or Arm B (FOLFIRI) in a 3:1 fashion.

4.1.1 Screening Phase

All patients will undergo screening assessments within 28 days prior to the first dose of study 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), current medications and procedures, ECOG performance status, hematology, 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 mandatory tumor biopsy prior to first dose of treatment will be

collected if 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 21-day cycles (Arm A) or continuous 28-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, CA 19-9 measurement, blood samples for research analyses and study drug administration and accountability. A mandatory on-treatment tumor biopsy will be obtained if considered safe and feasible.

Patients will be assessed for disease status per RECIST v1.1 after every 3rd cycle of treatment (Arm A) or every 2nd 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.

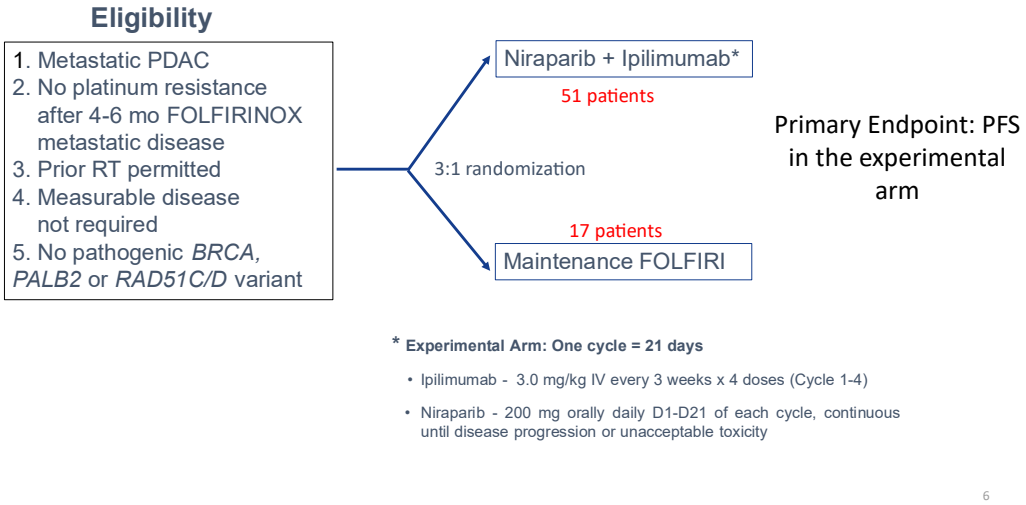
Assessments at this visit will include AEs, ECOG performance status, concomitant medications and procedures, physical examination, vital signs and weight measurements, hematology and serum chemistry, CA 19-9 measurement, research blood sample for research analyses, disease status assessment and study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

4.1.4 Follow Up Phase

Patients who received ipilimumab (Arm A) will have a 30-day and 90-day follow-up period for AEs following the last dose of study treatment. Please refer to the study calendar for details. Patients who received standard chemotherapy (Arm B) will have a 30-day follow-up for AEs following last dose of study treatment.

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. All patients will be followed for survival every six months until death, loss to follow-up, withdrawal of consent or until 5 years have passed, whichever occurs first.

4.1.5 Study Schema



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 Endpoint

The primary study endpoint will be progression-free survival (PFS) in the experimental arm, 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).

4.2.2 Secondary and Exploratory Study Endpoints

The secondary endpoints include:

- Evaluation of safety and tolerability of this combination as determined by CTCAE v5.0.
- Disease control, defined as achieving stable disease (SD), partial response (PR), or complete response (CR) per RECIST v1.1, in the experimental arm
- Overall response in the experimental arm (measurable patients only), defined as achieving partial or complete response (PR, CR) per RECIST v1.1.
- Overall survival, defined as time from randomization to death from any cause, in the experimental arm
- Disease control, progression free survival, overall response, and overall survival in the control arm

- of niraparib and ipilimumab in the experimental arm
- To determine biomarkers of response, mechanisms of action and immune pharmacodynamics of niraparib/ipilimumab in a population of patients with metastatic pancreatic cancer

Exploratory endpoints include:

- Systemic and tumor-specific determinants of response and resistance to maintenance therapy with niraparib and ipilimumab

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 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
- Participants must have received 8-12 cycles (4-6 months) of first-line FOLFIRINOX or modified FOLFIRINOX for metastatic disease with stable disease or better. Patients treated with liposomal irinotecan with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) are also eligible. Patients who were initially treated with FOLFIRINOX or NALIRIFOX but stopped oxaliplatin because of toxicity are eligible for the trial.
  - Note: This requires at least stable imaging and a stable or decreasing tumor marker as applicable and as determined by the investigator.
- Measurable disease is not a requirement for study entry

  -Note: The study will require that at least 80% of enrolled patients (i.e., 55 of all patients) are biopsiable at enrollment. The investigators may require measurable/biopsiable disease as the study progresses in order to achieve this goal.
- Participants must be willing to undergo a pre-treatment fresh tumor biopsy (if medically feasible).
- Participants must be willing to undergo an on-treatment tumor biopsy (if medically feasible).
- 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 (females) or 30 days (males) 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) ≤2.5 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, or other cytotoxic T-lymphocyte-associated-4 protein (CTLA-4) inhibitor.
- Patients who have demonstrated resistance to FOLFIRINOX are not eligible to participate in this study.
- Patients with known pathogenic/likely pathogenic germline or somatic alteration(s) in *BRCA1, BRCA2, PALB2, RAD51C,* or *RAD51D.*
- Patients with known mismatch repair deficiency or microsatellite instability-high cancer.
- 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.
- Patients with uncontrolled hypertension, defined as systolic BP >140mmHg and/or diastolic BP >90mmHg
- Patients with a prior history of posterior reversible encephalopathy syndrome (PRES).
- Acute infection requiring intravenous antibiotics, intravenous antiviral or intravenous antifungal agents during the 14 days prior to first dose of study therapy.
- Patients will be excluded if they have a history of or active 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 weeksof the first dose of study treatment.
- Patients must not be undergoing treatment for a second active cancer at the time of randomization. Exceptions include: (1) local therapies for skin cancers, (2) hormonal therapies for breast or prostate cancer without evidence of active disease Patients *may have* a history of: (1) adequately treated nonmelanoma skin cancers, (2) curatively treated in situ cancer of the cervix, (3) curatively treated DCIS, (4) curatively treated stage I, grade 1 endometrial carcinoma, (5) other solid tumors and lymphomas (without bone marrow involvement) diagnosed at least five years prior to randomization and treated with no evidence of disease recurrence
- Patients with active hepatitis B or hepatitis C infections, as defined by positive PCR testing, may not enroll.
- Patients with HIV may enroll, but must have an undetectable viral load at the time of enrollment and must be receiving a stable regimen of HAART.
- Patients must not have known, symptomatic brain or leptomeningeal metastases.

5.3 Patients or Partners of Patients with Reproductive Potential

Niraparib, ipilimumab, 5-fluourouracil and irinotecan should not be used during pregnancy or in women of childbearing potential (WOCBP) not using reliable contraception.

Women of childbearing potential should not become pregnant while on study treatment and may not be pregnant at the beginning of treatment.

Pregnancy Testing: A pregnancy test (blood or urine based on institutional preferences) should be performed on all WOCBP within 3 days prior to enrollment.

Contraception: Persons of childbearing potential must use effective contraception during therapy and for 6 mo (females) or 30 days (males) (nira/ipi) or three months (FOLFIRI) 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 who have 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 (Arm A) or 3 months (Arm B) 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 68 evaluable subjects will be enrolled between the University of Pennsylvania and at the Dana-Farber Cancer Institute.

5.5 Vulnerable Populations

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

6 STUDY INTERVENTION

Oral niraparib plus intravenous ipilimumab or maintenance FOLFIRI chemotherapy

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 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, for a total of four doses. 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: -5min/+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.

6.1.3 Rationale for Shorter Infusion Time for Ipilimumab

Long infusion times place a burden on patients and treatment centers. It is now established that ipilimumab can be safely administered using shorter infusion times of 30 minutes' duration. This will limit the burden to patients. Recent data has shown that ipilimumab can be safely administered over a 30 minute period with acceptably low incidence of infusion related reactions [16].

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

6.2 Intervention Regimen

6.2.1 Niraparib + Ipilimumab (Arm A)

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.

6.2.2 FOLFIRI (Arm B)

5-Fluorouracil, folinic acid, and irinotecan (FOLFIRI) will be administered as per standard institutional guidelines. Treatment is given every 14 days and each cycle is 28 days in length.

6.2.3 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 1-21 of each 21-day cycle.

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 Ipilimumab

The starting dose of ipilimumab will be 3mg/kg IV on days 1 of each 21-day cycle, for a total of four cycles.

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.

6.2.4.3 FOLFIRI

Chemotherapy will be given as per standard institutional guidelines.

6.2.4 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, no dose adjustments for the study medications are necessary.

For any toxicity leading to discontinuation of Niraparib 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. To ensure safety once drug has been resumed, 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 should undergo further hematologic investigation (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 Ipilimumab Dose Modifications

Table 5. GI Adverse Event Management Algorithm for 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 ¾
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 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 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 <u>If worsens:</u> • 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 <u>If improves:</u> • 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 <u>If not improving after 2 weeks or worsening:</u> • 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	<u>If improves to baseline:</u> • Taper steroids over at least 6 weeks <u>If not improving after 48 hours or worsening:</u> • Add additional immunosuppressi on

Table 8. Hepatic Adverse Event Management Algorithm for 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 that is 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 Ipilimumab

Asymptomatic TSH Elevation	• 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	
Symptomatic Endocrinopathy	• 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	<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
Suspicion of Adrenal Crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness)	• 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	

Table 10. Skin Adverse Event Management Algorithm for 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 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 of ipilimumab in subjects with mild and moderate hepatic impairment was similar to that of subjects with normal hepatic function.

6.2.5.3 Dose Modifications for FOLFIRI

Dose modifications for FOLFIRI will be performed per standard institutional guidelines at the discretion of the treating investigator.

6.2.5 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 anti-CTLA4 agents are not eligible to participate in this study. Patients who have demonstrated resistance of their pancreatic adenocarcinoma to FOLFIRINOX 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; review with an oncological pharmacist is recommended in these cases.
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 may be administered according to local guidelines and Section 6.2.5.1.

6.3.3 Bisphosphonates

Bisphosphonates are permitted.

6.3.4 Anticoagulants

Anticoagulants are permitted. The niraparib safety profile includes risk for thrombocytopenia; therefore, patients should be advised to use caution with anticoagulation and antiplatelet drugs.

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. However, if in the opinion of the investigator, the benefit of a non-live vaccine outweighs the risk to the patient, vaccines may be administered.

6.4 Warnings and Precautions

6.4.1 Niraparib

6.4.1.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML)

For the OC Pooled Safety Population in the monotherapy studies analysis, MDS/AML events were searched using MedDRA preferred terms for Myelodysplastic syndrome and Acute myeloid leukemia. In total, 26 niraparib-treated participants (1.9%) were reported to have MDS and/or AML as of the data cutoff, and all but one of these events were deemed related or likely related to study drug by the investigator. The majority of those participants were from the NOVA study (14 participants); 9 participants were in the PRIMA study, and 3 participants were in the QUADRA study. Three niraparib-treated participants experienced events of both MDS and AML, all related to treatment; in 1 of these participants, an event of AML was fatal.

Seven placebo-treated participants (1.7%) were reported to have MDS and/or AML (MDS, 5 participants; AML, 2 participants). In the niraparib-treated population, 26 participants (1.9%) experienced MDS/AML events (MDS, 17 participants [1.2%]; AML, 12 participants [0.9%]). These events were fatal in 9 participants (MDS, 4 participants [0.3%]; AML, 5 participants [0.4%]). Fatal SAEs of MDS were considered treatment-related in 4 participants (0.3%) of the niraparib-treated population. Fatal AML events were considered treatment-related in 4 participants (0.3%) of the niraparib-treated population. Grade 4 events of MDS that were considered treatment-related were reported in 6 participants (0.4%) in the niraparib-treated population. Grade 4 events of AML that were considered treatment-related by the Investigator were reported in 8 participants (0.6%) in the niraparib-treated population (includes 1 event of uncoded AML).

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 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 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 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 GSK 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 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 is an injectable drug that will be administered in the clinic by clinical nursing staff.

FOLFIRI is an injectable chemotherapy combination that will be administered in the clinic by 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.

It will not be considered a protocol deviation if a participant doesn't return their diary. The study team will utilize the pharmacy drug accountability records to determine compliance to the study medication.

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 + Ipilimumab)

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]	C1D8	C2D1	C3D1	C4D1	C5D1 and onward	EOT	30 Day FU	90 Day FU	LTFU
Informed Consent	X										
Randomization	X										
Demographics/ Medical History; Evaluation of previously performed germline and somatic sequencing[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 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	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			
CA 19-9 and/or CEA[t]		X			X	X		X			

Procedure[a]	Day -28 to Day -1 (unless otherwise specified)	C1D1[b]	C1D8	C2D1	C3D1	C4D1	C5D1 and onward[y]	EOT	30 Day FU	90 Day FU	LTFU
Serum Pregnancy Test (WOCBP only)	X			X	X	X	X				
HIV, Hepatitis B and C Testing	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]	X	X	X[v]	X[v]	X[v]			
Whole Blood		X[v]	X	X	X	X[v]	X[v]	X[v]			
Niraparib Dispensation, Administration, Accountability		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. Previously performed germline and somatic sequencing must be evaluated to ensure patient has no pathogenic germline or somatic variant in *BRCA1, BRCA2, PALB2, RAD51C* or *RAD51D*.

d = Height at screening only; not required if previously recorded in the medical record

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 and monthly for one year thereafter.**
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.
l = Disease assessments should be performed at fixed intervals of every 9 weeks (+/- 7 days). 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. Whenever possible, 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 4th 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 30 days prior to End of Treatment, a CT scan should be performed at the 30-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 4 day 1 if deemed safe and feasible +/- 7 days
s = All patients discontinued from treatment, regardless of reason, should be followed every six months 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, EMR review 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 PI. 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 and whole blood will be collected according to the site lab manual.
w= blood pressure 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 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.

7.2 Schedule of Assessments- ARM B (FOLFIRI)

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]	C1D8	D15 of all cycles	D1 of C2 and Beyond[y]	C4D1	EOT	30 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		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		X		
Serum Chemistry[i]	X[h]	X		X	X		X		

Procedure[a]	Day -28 to Day -1 (unless otherwise specified)	C1D1[b]	C1D8	D15 of all cycles	D1 of C2 and Beyond	C4D1	EOT	30 Day FU	LTFU
CA 19-9 and/or CEA[t]		X			X		X		
Serum Pregnancy Test (WOCBP only)	X								
HIV, Hepatitis B and C Testing	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[v]		X[u]		X[u]		
Whole Blood		X	X		X	X	X		
FOLFIRI Infusion		X		X	X		X		
Survival Status									X[s]

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. Please collect smoking history as part of medical history

d = Height at screening only

e = Vital signs (blood pressure, pulse, and temperature) to be taken pre-dose on clinic visit days.

f = AEs are recorded from the time of signing informed consent through 30 days after last dose of chemotherapy. 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.
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 = 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.
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. Whenever possible, 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 (i.e., odd numbered cycles starting with C3), or approximately every 8 weeks.
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 30 days prior to End of Treatment, a CT scan should be performed at the 30-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 at cycle 4 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, EMR review 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 = Blood samples for PBMC and whole blood will be collected according to the site lab manual.
v= PBMC research sample at C1D8 may be collected

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 history and status.
- Evaluation of germline and somatic sequencing results to ensure no pathogenic variants in *BRCA1, BRCA2, PALB2, RAD51C* or *RAD51D*.
- 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 treatment.
- 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 [Arm A only]) ≤7 days prior to the first dose of treatment.
- Serum pregnancy test for women of childbearing potential
- TSH (Arm A only)
- CA 19-9 and/or CEA (whichever is appropriate)
- HIV antibody
- Hepatitis B and C testing
- Tumor assessments should consist of clinical examination, appropriate imaging techniques including CT scans of the chest, CT or MRI of the abdomen and pelvis, with appropriate slice thickness per RECIST; other studies (X-ray, PET, and ultrasound) may be performed if required. Whenever possible, 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). 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 Cycle 1, Day 1 (Both Arms Unless Otherwise Specified)

- Physical Examination
- Weight
- ECOG performance status (16.1 Appendix A)
- Vital signs

  Arm A only: 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

  Arm A only: Weekly CBCs should be performed during the first four weeks of therapy and monthly for one year thereafter.
- Serum chemistries
- CA 19-9 and/or CEA measurement
- TSH and lipase measurements (Arm A Only)
- Correlative Research Blood samples will be obtained for PBMCs and Whole Blood on Cycle 1 Day 1, Cycle 1 Day 8 and every Cycle thereafter
- Adverse event monitoring
- The treatment core biopsy will be performed +/- 7 days of cycle 4, 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
- Niraparib dispensation (Arm A Only)
- Ipilimumab (Arm A; Cycles 1-4 only)) or chemotherapy (Arm B) administration

Arm A: 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 Cycle 1 Day 8

Patients will have blood drawn for PBMCs and for Whole Blood. These will be collected, processed and stored as per the Laboratory Manual.

7.4.3 Cycle 4 Day 1

If feasible and considered safe, every patient will undergo treatment-biopsy at C4D1, +/- 7 days.

7.4.4 Day 1 of Subsequent Cycles (Both Arms Unless Specified)

Arm A: Patients will be instructed to refrain from taking their first dose of oral niraparib prior to their clinic visits because certain assessments must be performed prior to dosing.

The following procedures will be completed prior to treatment on Day 1 of Each Cycle.

- Physical examination
- Weight
- ECOG performance status (16.1 Appendix A)
- Vital signs
  - Arm A Only: 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
- TSH and lipase measurements (Arm A only)
- CA 19-9 and/or CEA measurement
- Correlative Research Blood samples will be obtained for PBMCs and Whole Blood on Day 1 of each Cycle.
- Disease/ tumor assessment (using the same methodology as was used at screening [e.g., CT scan] whenever possible) prior to the start of every 3 cycles (Arm A) or every 2 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.
- AE monitoring
- Study drug accountability (Arm A only)
- Niraparib dispensation (Arm A only)
- Ipilimumab administration (Arm A only)
- Chemotherapy administration (Arm B only)

Arm A: 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.

7.4.5 Day 15 of Each Cycle (Arm B Only)

- Vital signs
- Adverse Events
- Hematology
- Serum Chemistry
- Chemotherapy Infusion

7.4.6 Tumor Assessments

Tumor assessments will be performed after every 9 weeks (+/- 7 days) 3rd cycle for Arm A and after every 8 weeks (+/- 7 days) for Arm B. Imaging should be performed prior to the first day of the next cycle of therapy.

7.4.7 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 and phosphate
- TSH measurement and lipase (Arm A only)
- CA 19-9 and/or CEA measurement
- Correlative Research Blood samples will be obtained for PBMCs, and Whole Blood
- 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 (Arm A only)

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 Day Follow-up Visit for MDS/AML (Arm A Only)

Patients who received niraparib (Arm A) will have intermittent monitoring for MDS/AML for up to 5 years as described in long-term follow up Section 7.7. Patients on this Arm 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 every 6 months for survival and MDS and/or AML (latter: Arm A only) until death, loss to follow-up, withdrawal of consent from study or for 5 years, whichever occurs first.

7.7.1 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. The study team must document in the subject record the decision to withdrawal and additional details including but not limited to if the subject withdraws consent from the entire study, and all research procedures to obtain data about the subject will be discontinued. The research study team may obtain follow-up data about the subject from publicly available records, e.g.: survival status. If the subject withdraws from the primary intervention and agrees to participate study assessments and/or allow for additional data collection through medical record review this should be documented in the subject record.

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, if possible.

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, if feasible. During this visit or when the subject is contacted, 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.
- Smoking history
- Detailed family history of all cancers
- Any previously performed genetic testing or sequencing results (of tumor tissue, circulating tumor DNA and/or germline) should be collected and stored

8.2 Physical Examination

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. 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) 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 [Arm A only] and lipase [Arm A only], 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 during the screening period.

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 every 3rd cycle (Arm A) or every 2nd 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, CT or MRI of the abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (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. Whenever possible, 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.

NOTE: Please note that a rising tumor marker in the absence of progressive disease on imaging is insufficient to determine disease progression.

8.8 Correlative Science

8.8.1 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 C4D1, if considered safe and feasible. Archival tissue will be collected whenever possible.

Blood draws for whole blood (for cytokine analysis) and peripheral blood mononuclear cells (PBMC) and Whole Blood will be collected at baseline and serially during therapy as noted above.

Tumor and blood samples will be processed according to the study Laboratory Manual.

8.8.2 Minimum Number of Required Biopsies

This protocol will enroll 51 patients in Arm A and 17 patients in Arm B, for a total of 68 patients. In order to perform the proposed correlative science, we will require that at least 80% of all patients (i.e. 55 patients total) undergo at least a baseline tissue biopsy.

At halfway through trial enrollment (i.e. once 34 patients have been enrolled), tissue acquisition rate will be assessed. Pending these results, the Principal Investigator and the Study Team may require that patients enrolled moving forward are required to have biopsiable disease as a Study Entry Criteria until the goal of 55 total baseline tissue samples is met.

8.8.3 Determining the impact of Immune Health on outcomes on nira/ipi (Wherry Lab)

Whole blood and PBMCs will be processed and stored in the Human Immunology Core (HIC) as per the Laboratory Manual.

Assays will be performed with a goal of understanding the circulating immune profile of patients who enroll on this study, and the impact that chemoimmunotherapy or chemotherapy alone has upon these patients, as can be detected in the peripheral blood. The methods will provide a comprehensive and accurate representation of the immune system and its dynamics in the setting of nira/ipi exposure, leading to new insights into determinants of treatment outcomes.

8.8.4 Defining the pharmacodynamic response and clinical impact of the immune microenvironment in nira/ipi treated tumors (Beatty and Wolpin-Nowak Labs).

Tissue samples will be processed and shipped to and/or stored in the Wolpin/Nowak and Beatty labs as per the Laboratory manual. The Wolpin laboratory will perform whole transcriptome spatial profiling. The Beatty laboratory will perform an evaluation of the lymphoid and myeloid cell phenotype, polarization, and spatial orientation in the PC microenvironment.

8.8.5 Investigating the role of cell proliferation and replication stress status in the response to nira/ipi (Wolpin-Nowak Lab).

The Wolpin/Nowak laboratory will use a multiplexed immunofluorescence panel in order to assess tissue samples for the status of key proteins and phosphoproteins in the DNA damage repair and cell cycle pathways.

8.8.6 Studying the impact of tumor transcriptional subtype on outcomes in nira/ipi treated tumors (Beatty and Wolpin-Nowak Labs).

The Beatty and Wolpin/Nowak laboratories will subtype tumors (i.e. basal, classical) using transcriptional subtypes and correlate this with treatment outcomes.

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. In addition, samples may undergo genomic and transcriptional analysis if there is available tissue.

9 STATISTICAL PLAN

This is a two-arm, open-label, randomized study of niraparib/ipilimumab with a non-comparative control arm of niraparib with maintenance FOLFIRI in patients with metastatic pancreatic adenocarcinoma who have achieved stability on FOLFIRINOX. The primary aim is to test the null hypothesis of mPFS 5mo versus the alternative hypothesis of an mPFS 7.5mo. With 68 patients enrolled over 14 months – 51 given niraparib/ipilimumab and 17 in the non-comparative control arm – and with 12 months of additional follow-up, there is 89% power for the test assuming exponential survival and 5% 1-sided type I error rate. With 17 control patients, a 90% confidence interval for any binomial parameter (toxicity, response, etc.) would be no wider than 43% percentage points and the chance of observing one or more rare events (4% true probability) is at least 50% and events of true frequency of 9% or higher have at least 80% probability of being observed (1 or more events out of 17 control patients).

9.1 Primary Endpoint

Progression-free survival in the experimental arm is the primary endpoint. Progression-free survival is 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). Median PFS and 95% confidence interval will be estimated from the Kaplan-Meier curve.

9.2 Secondary Endpoints

The secondary endpoints are:

(1) Overall response rate (ORR) in evaluable patients

(2) Overall survival (OS)

(3) PFS in the control arm

(4) OS in the control arm

(5) Overall response in evaluable patients within the control arm

(6) Safety

(7) To determine biomarkers of response, mechanisms of action and immune pharmacodynamics of niraparib/ipilimumab in a population of patients with metastatic pancreatic cancer

9.3 Sample Size and Power Determination

Sample size was chosen to detect a difference in 5 vs. 7.5 month median PFS in the experimental arm with 89% power and 5% 1-sided type-I error, then inflated to account for 3:1 randomization between the experimental and non-comparative control arms. Sample size was calculated assuming an exponential survival distribution in the experimental arm.

9.3.1 Statistical Methods

The primary analysis testing the null hypothesis of median PFS (mPFS) of 5 months versus mPFS of 7.5 months will be carried out using a Wald test assuming exponential survival, following Section 11.1 of Moore (2016). Suitability of the exponential distributional assumption will be assessed by plotting the Kaplan-Meier estimate of the survival function at each observed death times against the death times; if the assumption holds, we expect to see an approximately straight line. If the assumption does not hold, we will draw inference using the nonparametric confidence interval around the median survival estimate following Brookmeyer and Crowley (1982).

We will estimate the ORR in each arm as, at the end of the study, the proportion of patients who responded to treatment along with exact binomial 95% confidence intervals.

We will estimate median OS in each arm using the Kaplan-Meier estimate with 95% confidence intervals using Greenwood's formula.

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 mPFS is > 5 (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

10.3 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 Report Forms whether serious or not and reported to the Sponsor Investigator 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 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 follows:

Events not included in the NCI CTCAE will be scored as follows:
Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
Grade 4: Life Threatening: discomfort that represents immediate risk of death
Grade 5: Death related to AE.

10.4 Causal Relationship of Adverse Events to Study Drugs

All adverse events (AEs) must have their relationship to study therapy and/or interventions assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be considered. When assessing causality the investigator should reference the study documents such as protocol, informed consent, investigator brochure (s), package insert, relevant literature, and take into consideration the disease under study.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study therapy (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result,

occurs within a reasonable time after administration of the study therapy, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- Unrelated – The AE is completely independent of study therapy administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

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 treatment on trial (i.e. C1D1) through 90 days 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 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, the AE is otherwise explained, or the patient begins another anti-cancer therapy. 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 if they become aware 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 30 days of last dosing must be reported to the Penn Sponsor within 1 business day on a SAE 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 SAE form should be completed and reported to the UPenn Sponsor Investigator.

AEs, SAEs, or AESIs that occur during pregnancy will be assessed and processed according to the AE or SAE/AESI processes using the appropriate SAE 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 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 investigational products 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. In accordance with institutional and health authority requirements the sponsor investigator will make a 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 study specific Serious Adverse event form..

For additional 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 of the initial SAE. 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 Investigator. 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.

ACC Data Safety Monitoring Committee requires the investigator or their delegated study personnel to report:

- All grade 3 or higher events regardless of attribution or expectedness within 10 business days of knowledge.
- All unexpected deaths within two business day of knowledge.
- All other deaths within 30 days of knowledge. Deaths of subjects greater than 90 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

Please refer to the Study Manual of Procedures for additional reporting information.

10.15 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 will report per the local institutional policy requirements.

10.16 Investigator Reporting to Sponsor of Exceptions and Deviations

If the PI prospectively identifies a one-time, intentional action or process that departs from the IRB and CTSRMC approved study protocol (prospective deviation/exception), advanced documented IRB and DSMC approval is required. Please refer to the Study Manual of Procedures for additional information. The Sponsor Investigator will report to collaborators per contract and the FDA according to 21 CFR 312.

10.17 Medical Monitor

It is the responsibility of the Sponsor Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events. Medical monitoring by an independent clinician, Vivek Narayan, MD, Department of Medicine, Division of Hematology-Oncology will include a regular assessment of the number and type of serious adverse events on a periodic basis, as well as participate in decision-making regarding dose modifications, exemption and deviation requests and an ability to stop enrollment or the study for safety concerns. The Medical Monitor will contact the Director of the ACC DOCM and/or DSMC if there are concerns that are unable to be addressed by the PI.

10.18 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.

10.19 Data Collection and Management

This study will use Velos (PennCRMS) 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.”

10.20 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

This study will be monitored in accordance with the Abramson Cancer Center's (ACC) Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) Plan, approved by NCI during the Core Grant's most recent review. This plan requires that the investigator submit a study-specific plan outlining how data will be reviewed. In addition, the ACC Center's Department of Operations, Compliance and Monitoring (DOCM) will audit this study in accordance with their enhanced auditing program as outlined in the Study Manual of Procedures. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

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/GSK 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 and the proposed translational work will be supported by funds provided by the Lustgarten Foundation.

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.

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16 APPENDIX

16.1 Appendix A: ECOG

Table 14. 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 15. 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 16. 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 17. 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.