DF/HCC Protocol #: 18-207

TITLE: Phase 2 Proof-of-Concept Trial Testing the PARP Inhibitor Niraparib in Patients with Pancreatic Cancer Harboring Deficiencies in Homologous Recombination DNA Repair

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Study Exempt from IND Requirements per 21 CFR 312.2(b).

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SCHEMA

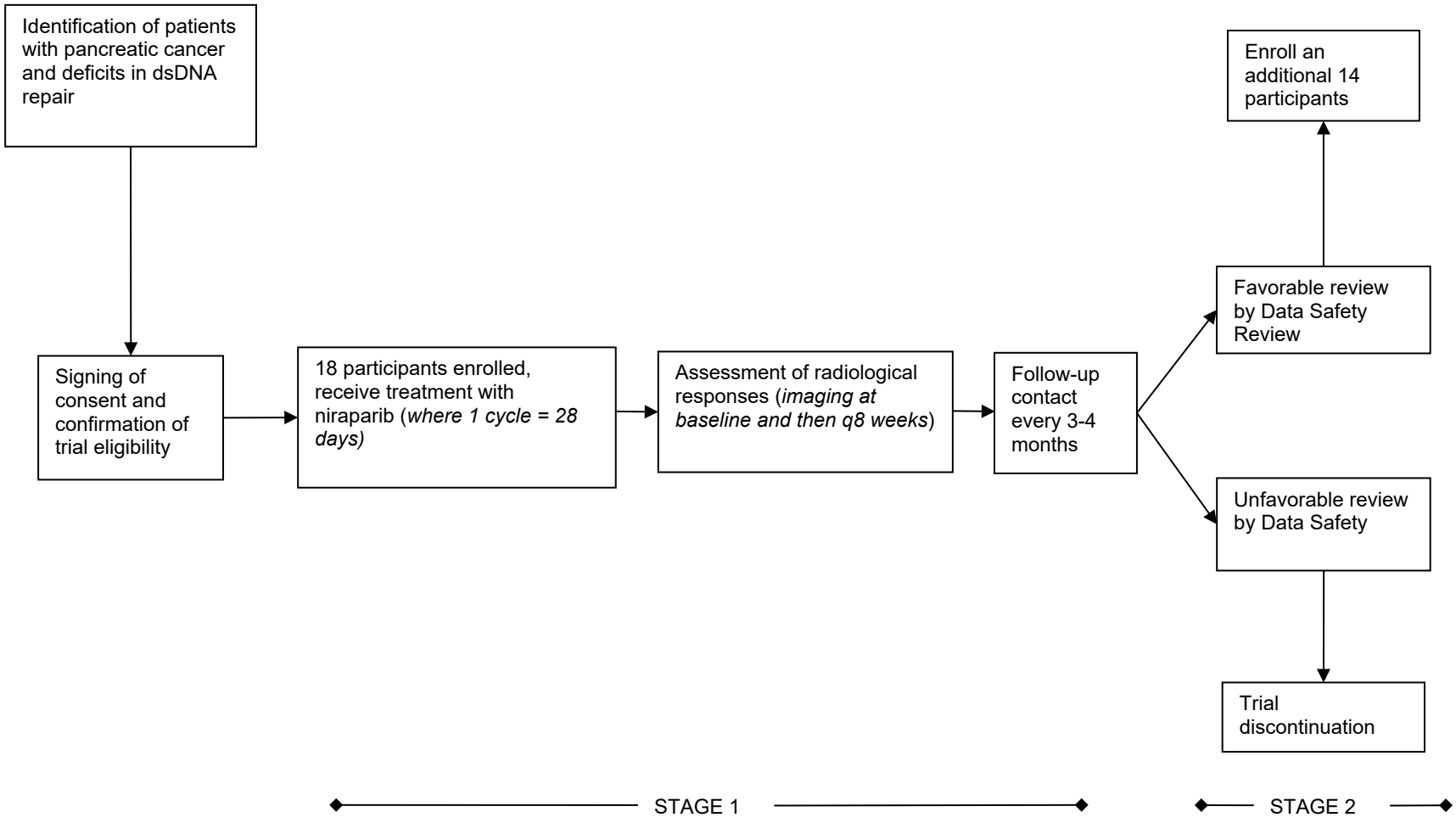

Identification of patients with pancreatic cancer and deficits in dsDNA repair
Signing of consent and confirmation of trial eligibility
18 participants enrolled, receive treatment with niraparib (*where 1 cycle = 28 days)*
Assessment of radiological responses (*imaging at baseline and then q8 weeks*)
Follow-up contact every 3-4 months
Enroll an additional 14 participants
Favorable review by Data Safety Review
Unfavorable review by Data Safety
Trial discontinuation
STAGE 1
STAGE 2

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OBJECTIVES

1.1 Study Design

This is an open-label, single-arm, non-randomized phase 2 clinical trial evaluating the anti-tumor activity of niraparib in patients with advanced pancreatic cancer harboring deficits in double stranded DNA (dsDNA) repair. The trial will employ a Simon 2-stage design, where 18 participants will be enrolled initially. Following enrollment of the first 18 patients, the Data Safety Monitoring Committee will meet to review the data of the trial. Based on this review, the Data Safety Monitoring Committee will determine whether an additional 14 patients can be enrolled.

1.2 Primary Objective

- To evaluate the efficacy of niraparib in patients with advanced pancreatic cancer who exhibit deficiencies in DNA homologous recombination (HR) repair, as measured by six-month progression-free survival (PFS).

1.3 Secondary Objectives

- Evaluation of the objective response rate
- Evaluation of the overall survival (OS) rate.
- Evaluation of the safety and tolerability of niraparib as assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
- Evaluation of the mechanisms of acquired resistance to niraparib by molecularly analyzing post-treatment tumor biopsies.
- Subset analysis of the response rate of niraparib in pancreatic cancers with germline mutations in DNA repair genes and somatic mutation of DNA repair genes.

2. BACKGROUND

2.1 Rationale

The multiple interdependent steps of DNA repair make it an ideal system to attack with a targeted agent. Seminal experiments from Farmer et al. and Bryant et al. demonstrated that combining deficiencies in single stranded DNA (ssDNA) repair and dsDNA repair by HR is synthetically lethal[1,2]. This preclinical observation led to the development of drugs that inhibit the PARP1 and PARP2 enzymes which play an important role in the repair of ssDNA breaks. Clinical development of PARP inhibitors has been focused on the most well-known population of patients with DNA HR deficits, patients with breast and ovarian cancer who have germline *BRCA1* and *BRCA2* mutations. Consistent with preclinical data, PARP inhibitors have been very well tolerated and have shown significant clinical activity in both *BRCA* germline (*BRCA*g) mutated breast and ovarian cancer[3-5]. The FDA has now approved three PARP inhibitors (niraparib, rucaparib, and olaparib) in ovarian cancer.

While the development of PARP inhibitors has been focused on patients with germline *BRCA1* and *BRCA2* mutations, data is emerging that suggests tumors harboring deficits in DNA HR other

than germline *BRCA* mutations would also be sensitive to PARP inhibitors. Preclinical data demonstrated that PARP inhibitors are effective in cells lacking proteins involved in HR and the DNA damage response. These proteins include RAD51B, RAD51C, RAD51D, RAD54, DSS1, RPA1, NBS1, ATR, ATM, PNKP, PALB2, CHK1, CHK2, CDK12, FANCD2, FANCA, FANCM,FANCC, BAP1, FANCE, FANCF, WRN, MRE11A, BLM, and BRIP1[6-13].

The success of PARP inhibitors in *BRCA*g mutated ovarian and breast cancer suggests that there may be opportunities to utilize PARP inhibitors in other cancers with deficits in dsDNA repair. Pancreatic cancer is a third leading cause of cancer-related mortality and new molecularly guided treatments are greatly needed. Germline mutations in *BRCA1*, *BRCA2*, and *PABL2* are known to cause familial pancreatic cancer[14,15]. A phase 2 trial recently demonstrated that olaparib has a response rate of 22% in 23 patients with *BRCA*g mutated pancreatic cancer[16]. The phase 2 RUCAPANC trial demonstrated that the rucaparib PARP inhibitor had an objective response rate of 15.8% in a population of pancreatic cancer patients with BRCA 1 and 2 germline or somatic mutations[22].

In addition to germline mutations in dsDNA repair, recent large-scale sequencing efforts demonstrated that a relatively large subset of pancreatic cancers have somatic deficits in DNA repair. In an analysis of 100 pancreatic adenocarcinomas that underwent whole exome sequencing (WES), approximately 20% of the cancers had a deficit in DNA repair[17]. Similarly, deficits in dsDNA repair were seen in 17% of 109 pancreatic adenocarcinomas analyzed with WES[18].

Based on this data, we propose a phase 2 clinical trial target of the niraparib PARP inhibitor in pancreatic cancer patients with deficits in dsDNA repair. If successful, this trial would be proof of principle that targeting DNA repair is a successful strategy in pancreatic cancer.

2.2 Niraparib (MK-4827)

2.2.1 Summary

Full niraparib background is available in the Investigator's Brochure (IB). Niraparib (formerly MK-4827) is an orally available, potent, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) -1 and -2 inhibitor. The crystalline tosylate monohydrate salt of niraparib is being developed as a monotherapy agent for tumors with defects in the HR DNA repair pathway and as a sensitizing agent in combination with cytotoxic agents and radiotherapy.

Niraparib is a potent and selective PARP-1 and PARP-2 inhibitor, with an inhibitory concentration at 50% of control (IC_{50}) of 3.8 nM (PARP-1) and 2.1 nM (PARP-2) and is at least 100-fold selective over other PARP family members. Niraparib inhibits PARP activity, stimulated as a result of DNA damage caused by addition of hydrogen peroxide, in various cell lines with an IC_{50} of about 4 nM and an IC_{90} of about 40 nM.

Niraparib demonstrates selective anti-proliferative activity for cancer cell lines that have been silenced for BRCA1 or BRCA2 or carry *BRCA1* or *BRCA2* mutations compared with their wild-type counterparts. The anti-proliferative activity of niraparib on *BRCA*-defective cells is a consequence of a cell cycle arrest in G2/M followed by apoptosis. Niraparib is also selectively cytotoxic for selected small cell lung cancer (SCLC) cell lines as well as for tumor cell lines

carrying homozygous inactivation of the *ATM* gene. Niraparib demonstrates weak activity on normal human cells. *In vivo* studies demonstrated strong anti-tumor activity with *BRCA1*-mutant breast cancer (MDA-MB-436), *BRCA2*-mutant pancreatic cancer (CAPAN-1), serous ovarian cancer (OVCAR3), and xenograft models in mice.

Target engagement was also demonstrated by measuring PARP activity in tumor homogenates from tumor xenograft studies. Inhibition of PARP activity has also been measured in peripheral blood mononuclear cells (PBMCs) from mice dosed with niraparib.

Niraparib has a low potential to be a victim of drug-drug interactions (DDI) in humans because it is a substrate of multiple metabolic enzymes, including the significant involvement of the non CYP (cytochrome P450) enzymes (i.e., carboxylesterases [CEs] and UDP glucuronosyltransferases [UGTs]). Oxidative metabolism of niraparib was primarily mediated by CYP3A4/5 and CYP1A2 with minor contribution from CYP2D6. Niraparib is a P-glycoprotein (P-gp) substrate and based on animal studies of oral administration, niraparib was observed to distribute to the central nervous system (CNS).

Niraparib was evaluated for its potential effects on cardiovascular and neurological function in dogs and mice, respectively. Niraparib inhibited human *hERG* current with an IC_{50} value of 10 μM and an IC_{20} value of 3.8 μM. QTc interval was unaffected; however, mean arterial pressure (up to 21% [3 mg/kg]) and heart rate (up to and 17% [10 mg/kg]) were increased; QRS cardiac interval was only increased at 10 mg/kg. Niraparib had no effect on neurological function in conscious mice at a single oral dose of 100 mg/kg. The cardiovascular changes observed with niraparib were relatively small and monitored in clinical studies.

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. Additionally, there have been rare reports of niraparib-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib.

To support the daily dosing of niraparib in humans, 1-month (2-week recovery period) and 3-month (28-day recovery period) repeat dose toxicity studies were conducted in rats and dogs. In all studies, hematotoxicities occurred but resolved by the end of the recovery period. In the rats, treatment-related arterial hypertrophy in heart and increased trabecula in the bone were noted, which did not demonstrate reversibility. Five rats on the high dose died, likely due to septicemia that occurred due to substantial cellular depletion in lymphoid organs and bone marrow. In the dogs, decreases in the amount of spermatogenic epithelium were considered reversible due to the continued presence of spermatozoa in all sections examined histomorphologically. Results from these studies indicated that increasing the dose duration from 1 month to 3 months did not cause new toxicity up to the MTD and that niraparib was well tolerated in animals.

Niraparib has been evaluated in a series of phase 1 clinical trials in patients with solid tumors. Thus far, 144 patients have been treated with niraparib at doses up to 400 mg once daily (QD) in

phase 1 studies. The dose-limiting toxicity (DLT) at this dose was thrombocytopenia; the MTD was determined to be 300 mg QD.

Pharmacokinetic (PK) properties determined across study cohorts were generally consistent, and exposures increased in a dose-related manner across the range of doses studied (30 to 400 mg).

Anti-tumor activity was observed in patients in the phase 1 studies taking niraparib as monotherapy at dose levels ranging from 60 to 400 mg. Based on investigator evaluation using RECIST v.1.1 and/or CA-125 criteria, an overall response rate of 13% was observed for all patients in this study. Analysis of the 20 *BRCA* mutant ovarian cancer patients enrolled in the study demonstrated that this group showed a 35% overall response rate.

Safety data from the phase 1 program suggest that treatment with niraparib is generally well tolerated. Preliminary safety data from 2 Phase 3 studies (including 1 blinded, placebo-controlled study) also suggest that treatment with niraparib is generally well tolerated.

Phase 3 Study of Niraparib Monotherapy in Platinum-sensitive, Recurrent Ovarian Cancer

In the randomized, double-blind, Phase 3 NOVA trial (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer), a total of 553 patients were randomized at 107 centers worldwide. Patients were categorized according to the presence or absence of a g*BRCA*mut (g*BRCA* cohort and non-g*BRCA* cohort) within their tumors and the type of non-g*BRCA*mut and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily (QD). The primary end point was PFS. The study enrolled 203 patients in the g*BRCA*mut cohort and 350 patients in the non-g*BRCA*mut cohort. Among the 350 patients in the non-g*BRCA*mut cohort, 162 had tumors that were identified as homologous recombination deficiency positive (HRDpos), and 134 had tumors that were HRD negative (HRDneg). HRD status was not determined for 54 patients.

Demographic and baseline characteristics were well balanced. Table 1 below shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (ie, g*BRCA*mut cohort, HRDpos cohort, and overall non-g*BRCA*mut cohort). In addition, median PFS in patients with HRDneg tumors was 6.9 months (95% confidence interval [CI]: 5.6, 9.6) in the niraparib arm, versus 3.8 months (95% CI: 3.7, 5.6) in the placebo arm, with a HR of 0.58 (95% CI: 0.361, 0.922) (p = 0.0226).

Table 1: Progression-Free Survival in Ovarian Cancer Patients in NOVA

	gBRCAmut Cohort		**Non-gBRCAmut Cohort (Regardless of HRD Status)**		**HRDpos (Within non-gBRCAmut Cohort)**	
	Niraparib (n = 138)	**Placebo (n = 65)**	**Niraparib (n = 234)**	**Placebo (n = 116)**	**Niraparib (n = 106)**	**Placebo (n = 56)**
Median PFS (95% CI)[(i)]	21.0 (12.9, NE)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value[(ii)]	< 0.0001		< 0.0001		< 0.0001	
HR (niraparib: placebo) (95% CI)[(iii)]	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	

Source: PR-30-5011-C (NOVA main) CSR
Abbreviation: CI = confidence interval; CSR = clinical study report; gBRCAmut = germline BRCA mutation; HR = hazard ratio; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; NE = not evaluated; PFS = progression-free survival.
[a] PFS is defined as the time in months from the date of randomization to progression or death.
[b] Based on stratified log-rank test using randomization stratification factors.
[c] Based on the stratified Cox proportional hazards model using randomization stratification factors.

The primary data to support the safety of treatment with niraparib are derived from the NOVA main study in which a total of 546 patients received study treatment.

All 367 patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). The high rate of TEAEs in the placebo group indicates the burden of prior chemotherapy and the patient's underlying ovarian cancer. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*mut and non-g*BRCA*mut cohorts. In the overall safety population, for the niraparib versus placebo treatment arms, the incidences of Grade 3 or 4 TEAEs (74% vs. 23%), serious adverse events (SAEs) (30% vs. 15%), TEAEs leading to treatment interruption (67% vs. 15%), TEAEs leading to dose reduction (69% vs. 5%), and TEAEs leading to treatment discontinuation (15% vs. 2%) were higher for niraparib than for placebo. There were no on-treatment deaths reported.

The most commonly observed nonhematologic TEAEs (all grades) observed in niraparib-treated compared with placebo-treated patients were nausea (74% vs. 35%), fatigue (46% vs. 32%), constipation (40% vs. 20%), and vomiting (34% vs. 16%). The majority of the nonhematological TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (all grades) of niraparib were anemia (49%), thrombocytopenia (46%), decreased platelet count (20%), and neutropenia (18%). Although Grade 3 or 4 hematologic laboratory AEs were common at the initiation of study treatment, no severe clinical sequelae were observed, and relatively few patients discontinued study treatment due to these AEs. Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these AEs beyond Cycle 3, indicating the overall effectiveness of the approach to dose modification. These TEAEs can be monitored routinely using standard assessments of hematological laboratory parameters, as is routine for patients with ovarian cancer receiving anticancer therapies. In the NOVA study, niraparib dose adjustment tended to occur early with most patients reaching their individual adjusted dose level at the end of Month 3 (i.e., Cycle 3) of treatment.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib. In the Phase 3 NOVA study, the incidence of MDS/AML in patients who received niraparib (5 of 367; 1.4%) was similar to its incidence in patients who received placebo (2 of 179; 1.1%). Guidance on monitoring patients for new AEs of MDS/AML and the follow-up of patients with suspected MDS/AML is provided.

Study PR-30-5011-C1 (NOVA corrected QT interval [QTc] sub study; n = 26) is an open-label evaluation of the effects of niraparib on QTc measurements in patients with histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. There were no

reports of clinically significant abnormal electrocardiogram (ECG) changes, including QTc interval prolongation, attributed to niraparib. Administration of niraparib at the therapeutic dose did not prolong the QT interval. There was no correlation between the exposure level (i.e., plasma concentration) of niraparib and QTc changes (i.e., change in corrected QT interval calculated using Fridericia's formula [ΔQTcF]).

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 baseline platelets had an impact on platelet nadir; lower baseline platelets (<180 10^9/L) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76%) or Grade ≥ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, Grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24%) compared to patients in the highest quartile (10%).

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

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

2.3 Genomic Eligibility

Eligibility for this trial requires that patients have a deficit in dsDNA repair. For purposes of this study, tumors with dsDNA repair deficiency can be demonstrated by germline DNA testing or somatic DNA testing. Pancreatic cancer patients with somatic or germline deleterious mutations in ATM, ATR, BAP1, BRCA1, BRCA2, CDK12, CHEK2 (CHK2), FANCA, FANCC, FANCD2, FANCE, FANCF, PALB2, NBS (NBN), WRN, RAD51B, RAD51C, RAD51D, MRE11A, CHEK1 (CHK1), BLM, BRIP1, IDH1, IDH2, RAD54L, BARD1, FAM175A, GEN1, XRCC2, SHFM1, and RPA1. are eligible to participate.

In recent years, in part because of the Supreme Court Ruling stating that *BRCA* genes could not be patented, there has been an increase in germline DNA testing for mutations in *BRCA1/2* as well as mutations in other genes involved in DNA HR repair. The Dana-Farber Cancer Institute's (DFCI) high risk genetics clinic routinely uses a commercially available multi-gene test which looks for germline mutations in DNA repair genes. Pancreatic cancer patients with deleterious germline mutations in ATM, ATR, BAP1, BRCA1, BRCA2, CDK12, CHEK2 (CHK2), FANCA, FANCC, FANCD2, FANCE, FANCF, PALB2, NBS (NBN), WRN, RAD51B, RAD51C, RAD51D, MRE11A, CHEK1 (CHK1), BLM, BRIP1, IDH1, IDH2, RAD54L, BARD1, FAM175A, GEN1, XRCC2, SHFM1, and RPA1. will be eligible for this trial.

Pancreatic cancer patients with somatic mutations in genes involved in DNA HR will also be eligible. We will primarily utilize the DFCI's OncoPanel testing. OncoPanel surveys the exonic DNA sequences of 447 cancer genes. Somatic mutations can also be identified through analyses of other commercially available and academic sequencing assays that are CLIA approved.

2.4 Correlative Studies Background

2.4.1 Tumor Tissue Collection

Patients enrolling on this trial will have received at least one line of prior treatment. Cytotoxic chemotherapy can cause genomic and functional changes that lead to PARP inhibitor resistance [19,20]. A pre-treatment tumor biopsy is mandatory from each patient enrolling on the trial. We believe that a pre-treatment tumor biopsy is necessary since functional and molecular characteristics of the HR pathway may change with therapy, and therefore it is essential for the sake of the analysis to confirm that patients exposed to niraparib have a deficiency in the HR pathway. Results of these pre-treatment biopsies will not affect eligibility but will be a central component of the analysis. We will closely analyze the pre-treatment tumor biopsy to evaluate if there have been acquired mutations in DNA HR genes since this is a known potential resistance mechanism to PARP inhibitors[19,20].

In order to further the understanding of acquired resistance to PARP inhibitors, participants who achieve clinical benefit on trial will be offered an optional post-treatment tumor biopsy at the time of disease progression.

Core needle, incisional, or excisional biopsies may be obtained for analysis at the time points indicated below. Biopsy procedures will be performed following standard institutional procedures. The tissue collection goal is 3 – 6 core biopsy samples collected using an 18 - 20-

gauge needle. Less than the goal amount of tissue is acceptable and should be based upon the clinical judgment of the treating investigator and the clinician performing the procedure. In the event tissue is insufficient for analysis it will not be considered a protocol violation.

- Biopsy #1 (Pre-Treatment): A mandatory fresh tumor tissue biopsy will be obtained pretreatment from all participants.
    - The pre-treatment fresh tumor biopsy may be obtained any time before the participant's Cycle 1 Day 1 visit.
- Biopsy #2: An additional optional biopsy at the time of disease progression will be offered to all participants.
    - The time of progression biopsy should be obtained prior to the initiation of another anti-cancer therapy when possible. In the event this is not feasible, the time of progression biopsy may be obtained up to 30 days after the date that disease progression was determined. The date of progression may be considered either the date the radiological scan was performed, or the date the treating investigator judged the participant to have progressed.

Biopsy tissue will undergo whole exome sequencing (WES) at the Broad Institute. The Broad Institute has generated a total of over 2,500 x 10^{12} bases (2,500 Terabases) of sequence data using next-generation sequencing (NGS). The Broad Institute has substantial experience with WES, and in fact invented one of the most commonly used approaches available today[21]. The protocol involves generating tens of thousands of 120-mer oligonucleotides on solid arrays, cleaving them from the array and converting them into single-stranded, biotin-labeled RNA "baits" to drive hybridization through high concentration. This protocol has been licensed to Agilent, and this method has now been used in more than 500 publications.

The sequencing platform of the Broad Institute boasts 50 Illumina HiSeq instruments and 10 MiSeqs, for an average capacity of 2.1 Terabytes (spanning 6192 flow cells) per day. The whole-exome panel includes: 18,557 genes (selected from RefSeq CDS) comprising 185,915 exons and 33 Mb of target. These targets are covered by 277,944 oligo "baits." A new exome-wide bait set is being adapted that allows even sequence coverage per capture reaction; this innovation will allow the sequencing of clinical tumor samples to a sufficient overall mean coverage, while preserving the overall sensitivity and specificity of variant calling.

To perform WES, nucleic acid (DNA and RNA) will be obtained from tumor cellular material using standard operating procedures in common use at the Broad Institute. For clinical tumor specimens, a "high-coverage" sequencing approach is utilized, which should yield an average coverage of 150-200 fold; paired normal DNA will be sequenced to a depth of approximately 80 to 100-fold. WES data will be analyzed for base mutations, small insertions/deletions, and copy number alterations.

In parallel, the Broad Genomics Platform will perform whole transcriptome sequencing. The Broad Genomics Platform has extensive experience with whole transcriptome sequencing from both frozen and FFPE tumor samples. Regarding the latter, transcriptome capture is an alternative to traditional transcript enrichment methods (including polyA selection and ribosomal depletion) that is optimal for low-input and degraded samples including formalin-fixed paraffin embedded (FFPE) tissues. The approach first prepares a stranded cDNA library from isolated

RNA, and then hybridizes the library to a set of DNA oligonucleotide probes to enrich the library for mRNA transcript fragments. Transcriptome Capture targets 21,415 genes, representing 98.3% of the RefSeq exome. In biological scenarios this assay has achieved expected results. For example, in one patient tumor at three time points, the third time point manifested robust KRAS amplification in the DNA that had concomitant over-expression of KRAS in the RNA from that same tumor.

WES of tumor tissue obtained pre-treatment and at the time-of-progression, along with tumor-derived circulating free DNA (cfDNA) from blood, will be used to evaluate whether there are genomic alterations that may be associated with improved clinical outcome with niraparib therapy and to assess for mechanisms of resistance.

2.4.2 Functional assay for homologous recombination proficiency in the pre-treatment biopsy sample

RAD51 nucleofilament formation is a vital step during homologous recombination (HR) mediated DNA damage repair. Such RAD51 nucleofilaments are detected as sub-nuclear foci by immunohistochemistry for RAD51. Presence of RAD51 foci is a functional read-out for HR proficiency. FFPE sections of the pretreatment biopsy will be stained using antibodies to RAD51, gamma-H2AX and GEMININ. Presence of RAD51 foci indicates that the tumor sample is HR proficient. Pan-nuclear RAD51 staining without evidence of foci or lack of RAD51 staining indicates that the tumor is HR deficient. Since HR occurs during the S-phase of the cell cycle, staining for GEMININ, a marker for S-phase, will be used to estimate the percentage of S-phase cells in the sample. RAD51 foci are present in a fraction of S-phase cells in HR proficient tumors. Percentage of cells that stain positive for gamma-H2AX is a measure of endogenous level of DNA damage. Lack of RAD51 foci and higher percentage of cells with gamma-H2AX staining are indicators of HR deficiency.

2.4.3 Organoid Culture Generation

Any remaining tissue from the pretreatment biopsy will also be utilized for generation of organoid cultures. Scientists from Dr. Brian Wolpin's group at the Dana-Farber Cancer Institute and Broad Institute have recently found a high success rate in growing organoid cultures from pancreatic cancer tumor biopsies. These organoid cultures function as important model systems to study mechanisms of PARP inhibitor resistance and sensitivity in pancreatic cancer.

2.4.4 Circulating free DNA Collection

Blood sample collections will occur at baseline, on day 1 of each subsequent cycle, and at the off-study visit. Each blood sample would be processed for cfDNA and germline DNA. The extraction of cfDNA and germline DNA will be performed from frozen aliquots of plasma and white blood cells, respectively. The yields and purities of cfDNA will be assessed prior to WES. It has been recently demonstrated that the yield and purity of cfDNA is adequate for sequencing (25-30%) with variance in the quantity through the course of therapy. DNA samples will be subjected to the same WES analysis at the Broad Institute described above. In addition to evaluating genomic alterations in DNA extracted from blood, the findings will be compared to parallel sequencing analysis done on tissue biopsies from the same subjects to compare similarities and any potential differences. This analysis will help us to determine whether cfDNA sequencing may be a possible substitute for tissue-based sequencing which would be

critical, as tissue biopsies are both invasive and costly. We will also evaluate quantitative changes in tumor-derived cfDNA through the course of therapy to determine correlation with tumor burden and clinical outcome on study.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have a histologically confirmed advanced pancreatic adenocarcinoma that is not curable with standard approaches. Patients with metastatic pancreatic cancer and unresectable pancreatic cancer are eligible.

3.1.2 Patients must have molecular characteristics that fulfill one of the following requirements:

- Germline deleterious ATM, ATR, BAP1, BRCA1, BRCA2, CDK12, CHEK2 (CHK2), FANCA, FANCC, FANCD2, FANCE, FANCF, PALB2, NBS (NBN), WRN, RAD51B, RAD51C, RAD51D, MRE11A, CHEK1 (CHK1), BLM, BRIP1, IDH1, IDH2, RAD54L, BARD1, FAM175A, GEN1, XRCC2, SHFM1, and RPA1. mutations. Germline variants of unknown significance are not eligible.
- Somatic mutation in ATM, ATR, BAP1, BRCA1, BRCA2, CDK12, CHEK2 (CHK2), FANCA, FANCC, FANCD2, FANCE, FANCF, PALB2, NBS (NBN), WRN, RAD51B, RAD51C, RAD51D, MRE11A, CHEK1 (CHK1), BLM, BRIP1, IDH1, IDH2, RAD54L, BARD1, FAM175A, GEN1, XRCC2, SHFM1, and RPA1.
- Germline and somatic testing need to be performed in CLIA approved laboratories. Deleterious genetic mutations should either be described in the literature or felt by expert opinion (in consultation with the principal investigator) to interfere with the protein's DNA repair function. The somatic mutational testing can be performed on tissue samples taken from any time in the patient's pancreatic cancer history.

3.1.3 Patients must have received at least one line of treatment for their cancer prior to enrolling on the trial. Patients who received adjuvant or neoadjuvant therapy are eligible for the trial if their cancer recurs within 6 months of completing therapy.

3.1.4 Patients who had investigator assessed progression on an oxaliplatin-containing regimen (such as FOLFOX or FOLFIRINOX) are not eligible for the trial.

3.1.5 Age ≥ 18 years. As no dosing or adverse event data are currently available in participants < 18 years of age, children are excluded from this study.

3.1.6 ECOG performance status of 0 or 1 (see **Appendix A**)

3.1.7 Participants must have adequate organ and marrow function as defined below:

– Absolute neutrophil count	≥ 1,500/mm^3
– Platelets	≥ 100,000/mm^3
– Hemoglobin	≥ 9g/dL
– Total bilirubin	≤ 1.5 × institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN
– Serum creatinine	≤ 1.5 × institutional ULN **-OR-**
– Creatinine clearance	≥ 30 mL/min/1.73 m^2 for participants with serum creatinine levels above the institutional ULN
– Albumin	≥ 2.7 g/dL

3.1.8 Female participants must have a negative serum pregnancy test within 3 days prior to taking study treatment if of childbearing potential and agrees to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment, or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):

- ≥45 years of age and has not had menses for >1 year
- Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range (>35µlU/mL) upon screening evaluation
- Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. See Section 5.5 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

3.1.9 Participant must agree to not breastfeed during the study or for 180 days after the last dose of study treatment.

3.1.10 Male participant agrees to use an adequate method of contraception (see Section 5.5 for a list of acceptable birth control methods) starting with the first dose of study treatment through 180 days after the last dose of study treatment. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

3.1.11 Participant must agree to not donate blood during the study or for 90 days after the last dose of study treatment.

3.1.12 Ability to swallow and retain oral medication.

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

3.1.14 Participants must be willing to undergo a pre-treatment fresh tumor biopsy. The biopsy requirement can be waived only after discussion with the principal investigator.

3.1.15 Participant receiving corticosteroids may continue as long as their dose is stable for least 4 weeks prior to initiating protocol therapy.

3.1.16 Patients must have normal blood pressure or adequately treated and controlled hypertension. (i.e. systolic BP ≤ 140 mmHg and diastolic BP ≤ 90 mmHg

3.2 Exclusion Criteria

3.2.1 Participants who have had cytotoxic chemotherapy, radiotherapy, immunotherapy, biologic therapy within 2 weeks prior to entering the study or those who have not recovered to ≤ CTCAE (version 5.0) Grade 1 or baseline from adverse events due to agents administered more than 2 weeks earlier (with the exceptions of alopecia and peripheral neuropathy).

3.2.2 Participants must not have received investigational therapy administered ≤ 3 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior initiating protocol therapy.

3.2.3 Participants who have received oral targeted therapy or tyrosine kinase inhibitor (TKI) therapy within 5 half-lives or 2 weeks of study entry, whichever is shorter.

3.2.4 Participants who have been previously treated with a PARP inhibitor.

3.2.5 Participant has had radiation therapy encompassing >20% of the bone marrow within 2 weeks; or any radiation therapy within 1 week prior to Day 1 of protocol therapy.

3.2.6 Participants who have undergone major surgery ≤ 3 weeks prior to initiating protocol therapy. Participants must have sufficiently recovered from adverse events caused by the procedure as judged by the treating investigator.

3.2.7 Participants with known untreated brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Participants with a history of brain metastases that have been treated, are no longer taking corticosteroids, and have been stable on imaging for ≥ 4 weeks following the last date of treatment are permitted.

3.2.8 History of hypersensitivity to compounds of similar chemical or biologic composition to niraparib or its excipients.

3.2.9 Participants must not be immunocompromised. Participants with prior splenectomy are allowed.

3.2.10 Participants must not have received a transfusion (platelets or red blood cells) ≤ 4 weeks prior to initiating protocol therapy.

3.2.11 Participant must not have any known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)

3.2.12 Participants must not have current evidence of any condition, therapy, or laboratory abnormality (including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]) that might confound the results of the study or interfere with the participant's participation for the full duration of the study treatment or that makes it not in the best interest of the participant to participate.

3.2.13 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.14 Known HIV-positive participants are ineligible because these participants are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.15 Participants with a clinically significant gastrointestinal disorder that in the opinion of the treating investigator could impact the absorption of the study drug, including but not limited to malabsorption syndrome or major resection of the stomach or bowels.

3.2.16 Participants with a history of a clinically relevant second primary malignancy within the past 2 years. Exceptions include: resected basal and squamous cell carcinomas of the skin and completely resected carcinoma *in situ* of any type.

3.2.17 Participants must not be on anticoagulant therapy unless the treating investigator has deemed it safe to temporarily hold to facilitate the collection of the pre-treatment tumor biopsy.

3.2.18 Participant must not have received colony stimulating factors (eg, granulocyte colony-stimulating factor, granulocyte macrophage colony stimulating factor, or recombinant erythropoietin) within 4 weeks prior initiating protocol therapy.

3.2.19 Participant 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.

3.2.20 Participant received a live or live-attenuated vaccine ≤14 days before first niraparib dose.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

Niraparib will be administered at 200mg or 300 mg by mouth once daily continuously beginning on Cycle 1 Day 1, with 28 consecutive days defined as a treatment cycle. Treatment will be

administered on an outpatient basis. Reported adverse events and potential risks are described in **Section 7**. Appropriate dose modifications are described in **Section 6**.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy, with the exception of palliative radiation therapy to a small field >1 week prior to Day 1 of study treatment (excluding the pelvic region and/or palliative radiotherapy encompassing > 20% of the bone marrow within 2 weeks of the first dose of study treatment) which may be administered after the 1st restaging scan has occurred 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. In the event radiation, will be administered, niraparib should be held for the duration of the radiation treatment and until toxicity associated with the radiation has resolved to ≤ Grade 1 or baseline. Bisphosphonate use is permitted.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Patients who completed screening assessments > 96 hours prior to cycle 1 day 1 should have cycle 1 day 1 laboratory values that re-meet eligibility criteria. If screening assessments were completed ≤ 96 hours prior to cycle 1 day 1, laboratory tests do not need to be repeated on cycle 1 day 1 and the screening laboratory values can be used as the cycle 1 day 1 values.

5.2.2 Subsequent Cycles

Management of specific toxicities considered at least possibly related to the study regimen is outlined in **Section 6.3.**

5.3 Agent Administration

Participants will take niraparib as a flat-fixed, continuous daily dose according to the Table 1 below. Niraparib can be taken with or without food. Participants should take doses at approximately the same times each day. Bedtime administration may be a potential method for managing nausea. Doses of niraparib should be taken approximately 24 hours apart. Missed doses should not be made up if it has been greater than 12 hours from the previous dose. Doses that would be outside of this time range should be considered missed and should not be taken. Vomited doses should not be retaken. Niraparib capsules should be swallowed whole and should not be chewed, crushed, opened, or dissolved.

If niraparib is dose reduced, participants should be instructed to continue using their current supply at their new dose until their supply has been exhausted.

Participants must be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed and documented.

Table 1: Niraparib Dosing

Baseline Criteria	Starting Dose
≥77 kg **and** Platelets ≥150,000 mm3	300 mg (3 X 100 mg capsules) or daily
<77 kg **or** Platelets <150,000 mm3	200 mg (2 X 100 mg capsules) or daily*

* For patients whose starting dose is 2 capsules once daily, escalation to 3 capsules once daily is permitted if no treatment interruption or discontinuation was required during the first 2 cycles of therapy

5.4 General Concomitant Medication and Supportive Care Guidelines

Investigators should use appropriate supportive medications to address toxicities that arise during the study, including but not limited to antiemetics, antidiarrheals, and blood product transfusion. No investigational or commercial agents or therapies other than niraparib may be administered with the intent to treat the participant's malignancy. Of note, bisphosphonate use is permitted.

In vitro studies suggested that niraparib was not a potent reversible inhibitor of CYP1A2, CYP3A4/5, or other drug-metabolizing CYP members including CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 (IC_{50} >70 μM). In addition, niraparib was not a time-dependent inhibitor of CYP3A4/5 at concentrations up to 50 μM. Therefore, niraparib is not expected to cause CYP-mediated drug-drug interaction (DDI) *in vivo*. In addition, niraparib is unlikely to be the victim of DDI as a substrate for multiple drug-metabolizing enzymes including the members of CYP and non-CYPs (i.e., CEs and UGTs).

Niraparib did not induce CYP3A4 expression at drug concentrations up to 20 μM in human hepatocytes. However, niraparib weakly elevated the activity of CYP1A2 in a concentration-dependent manner, with a maximum elevation of approximately 26% relative to omeprazole at ≥5 μM. Therefore, the potential for auto-induction in niraparib metabolism is expected to be minimal.

In view of the multiple pathways involved in the biotransformation of niraparib and the lack of either inhibitory or inducibility potential towards CYP3A4, the risk of a PK interaction between niraparib and the substrates and modulators (inhibitors or inducers) of CYP3A4 is highly unlikely. Caution is recommended when niraparib is combined with active substances the metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (eg, clozapine, theophylline, and ropinirole).

Table 2: Drugs Known to Inhibit or Induce CYP1A2 and the Substrates of CYP1A2		
Inhibitors of CYP1A2		
Strong ≥5-fold increase in AUC or >80% decrease in CL	**Moderate** ≥2 but <5-fold increase in AUC or 50%-80% decrease in CL	**Weak** ≥1.25 but <2-fold increase in AUC or 20%-50% decrease in CL
Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine,	Acyclovir, allopurinol, caffeine, cimetidine, daidzein, disulfiram, Echinacea, famotidine,

Table 2: Drugs Known to Inhibit or Induce CYP1A2 and the Substrates of CYP1A2		
	thiabendazole, vemurafenib, zileuton	norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
Inducers of CYP1A2		
Strong 80% decrease in AUC	**Moderate** 50%-80% decrease in AUC	**Weak** 20%-50% decrease in AUC
	Montelukast, phenytoin, smokers versus non-smokers	Moricizine, omeprazole, phenobarbital
Substrates of CYP1A2		
Sensitive Substrates[a]	**Substrates with Narrow Therapeutic Range[b]**	
Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine	
a. Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor or AUC ratio in poor metabolizers vs. extensive metabolizers is greater than 5-fold. b. CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes). *Guidance for Industry, Drug Interaction Studies, February 2012*		

Nonclinical and clinical cardiovascular studies did not identify a risk for QT interval prolongation. There were no clinically relevant changes in other electrocardiogram (ECG) parameters or abnormal ECG findings attributable to the administration of niraparib
The niraparib safety profile includes risk for thrombocytopenia; therefore, treating investigators should use caution with anticoagulation and anti-platelet drugs.

Prophylactic cytokines (i.e., granulocyte colony-stimulating factor [GCSF]) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current American Society of Clinical Oncology (ASCO) guidelines.

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

Participants must not breast-feed while receiving protocol therapy and for 180 days following the last dose of protocol therapy.

Participants must not donate blood during the study or for 90 days after the last dose of protocol therapy.

Patients must not receive live or live-attenuated vaccines during niraparib treatment or within 14 days following completion of niraparib treatment.

5.5 Acceptable Methods of Contraception

Participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation beginning with time of consent, during the study treatment and for 180 days after last dose of study treatment(s):

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral route
  - Intravaginal route
  - Transdermal route
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence, if the preferred and usual lifestyle of the subject

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Pregnancy
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Investigator becomes aware of conditions or events that suggest a possible hazard to patients if the clinical study continues
- Patient is diagnosed with MDS or AML (as confirmed by a hematologist) or Posterior Reversible Encephalopathy Syndrome

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, James Cleary MD, PhD at 617-632-6073.

5.7 Duration of Follow Up

Participants will be followed until death after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:
- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Termination of study

For participants who are thought to be lost to follow-up, at least 3 documented attempts, including 1 via certified mail, should be made to contact the participant before the participant is deemed lost to follow-up.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Decentralized Subject Registrations, the research team updates the relevant Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS/ DISCONTINUATION

Dose delays and modifications will be made as indicated in the following table. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

6.1 Dosing Delays

Any toxicity observed during the course of therapy may be managed by interruption of the dose if deemed appropriate by the treating investigator. Additionally, dose interruptions may be required as described in **Section 6.3** below. Niraparib may be held for a maximum of 28 days, participants requiring a longer delay should be removed from protocol therapy. Participants who are deriving clinical benefit who require a longer hold may be allowed to continue on treatment following discussion and agreement with the Overall Principal Investigator.

If a participant's dosing is held mid-cycle, the counting of cycle days and assessment schedule will continue without interruption. For example, a participant who does not receive their Cycle 3 Day 19 – Cycle 3 Day 21 doses due to toxicity will restart dosing on Cycle 3 Day 22 and proceed with their next scheduled visit as previously planned (Cycle 4 Day 1). Interim visits may be conducted as clinically necessary to manage toxicity; however, the cycle will not restart for dosing delays due to adverse events. Participants who require a delay at the start of the cycle may have their cycle start delayed, so that the day they resume dosing will be considered Day 1 of the next cycle.

6.2 Dose Modifications

Dose interruption and/or modification of niraparib may be implemented due to nonhematologic or hematologic toxicities per the Investigator's judgement after Cycle 1.

Treatment must be interrupted for any nonhematologic Common Terminology Criteria for Adverse Events (CTCAE version 5.0) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib (Table 3). If the nonhematologic toxicity is appropriately resolved to baseline or Grade ≤1 within 4 weeks (28 days) of the dose interruption period, the patient may restart treatment with niraparib but with a dose level reduction if prophylaxis is not considered feasible (see Table 4). If the event recurs at similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made according to Table 3.

If the toxicity requiring dose interruption has not resolved completely or to CTCAE Grade 1 during the maximum 4-week (28-day) dose interruption period, and/or the patient has already undergone a dose reduction to a minimum dose of 100 mg QD, the patient must permanently discontinue treatment with niraparib.

The dose interruption and modification criteria for niraparib for hematologic parameters will be based on blood counts and are outlined in Table 8. If the hematologic toxicity has not recovered

to the specified levels within 4 weeks (28 days) of the dose interruption period, the patient must permanently discontinue treatment with niraparib.

For patients whose initial dose is 3 capsules daily (300 mg/day), dose reductions to 2 capsules daily (200 mg/day) and subsequently to 1 capsule daily (100 mg/day) will be allowed. No further dose reduction will be allowed.

For patients whose initial dose is 2 capsules (200 mg/day), dose reduction to 1 capsule once daily (100 mg/day) will be allowed. No further dose reduction will be allowed.

Table 3: Recommended Dose Modifications for Adverse Reactions

Dose level	**Initial Dose: 3 capsules per day**	**Initial Dose: 2 capsules per day**
Starting dose	3 capsules once daily (300 mg/day)	2 capsules once daily (200 mg/day)
First dose reduction	2 capsules once daily (200 mg/day)	1 capsule once daily (100 mg/day)
Second dose reduction	1 capsule once daily (100 mg/day)	Discontinue

Table 4: Niraparib Dose Modifications for Nonhematologic Adverse Reactions

Abnormality	**Intervention**
Non-hematologic CTCAE ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. Resume niraparib at a reduced dose.
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue niraparib.
Confirmed PRES	Discontinue niraparib.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events (Version 5.0). PRES = Posterior Reversible Encephalopathy Syndrome

Table 5: Niraparib Dose Modifications for Hematologic Toxicity

Laboratory Abnormality	Intervention
Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time.	
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 investigator discretion using dose reduction guidelines in Table 3. If platelet count is < 75,000/μL, resume niraparib when platelet count returns to ≥ 100,000 at a reduced dose per Table 3.
	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 per Table 3. 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 count < 1,000/μL	Withhold niraparib for a maximum of 28 days and monitor blood counts until neutrophil counts return to ≥1,500/μL. Resume niraparib at a reduced dose per Table3. 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 maximum dose reductions per Table 3.
Hemoglobin ≤ 8 g/dL	Withhold niraparib for a maximum of 28 days and monitor blood counts until hemoglobin returns to ≥9 g/dL. Resume niraparib at a reduced dose per Table 3. 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 maximum dose reductions per Table 3.
Hematologic adverse reaction requiring red blood cell and/or platelet transfusion	For participants 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. RBC transfusion is at the discretion of the Investigator. Resume niraparib at a reduced dose per Table 3.
Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.

Abbreviation: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; QD = once daily.

In the case of thrombocytopenia, following the first occurrence, resumption of therapy may occur at the same dose or 1 dose level lower when the hematologic toxicity has resolved. Subsequent occurrences should trigger dose reduction upon resumption of therapy. If the platelet count has not reverted within 28 days of interruption to ≥100,000/μL, then study treatment should be discontinued.

If dose interruption and/or modification is required at any point during study treatment because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until the AE resolves to the specified blood count levels. To ensure the safety of the new dose, weekly blood draws for CBC will be required for an additional 4 weeks after the AE has resolved, after which monitoring every 4 weeks may resume. CBC monitoring will continue every 4 weeks (i.e., monthly) for the next 11 months of treatment, and periodically after this time.

If a patient develops severe persistent hematological toxicity including pancytopenia that does not resolve to thresholds as defined in Table 5 within 28 days following interruption, niraparib should be discontinued.

Any patient requiring transfusion of platelets or red blood cells (≥1 unit) must undergo a dose reduction upon recovery if study treatment is resumed (Table 5).

If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue study treatment.

For major surgery while on study treatment, up to 4 weeks (28 days) of study treatment interruption is allowed.

6.3 Toxicity Management

Management of toxicity considered at least possibly related to treatment with niraparib in the opinion of the treating investigator is detailed in **Table 4** and **Table 5**.

6.4 Evaluation of Possible MDS/AML

Any patient with suspected MDS/AML, either while a patient is receiving treatment or during for post-treatment assessments, should be referred to a local hematologist, who must perform bone marrow aspirate and biopsy testing. Testing completed as part of standard of care is sufficient. Report data will be entered in the appropriate eCRF pages and the site must keep a copy of all reports with the patient's study file.

6.5 Overdose Management

There is no known antidote for over-dosage of niraparib. In case of suspected overdose, monitor hematology, chemistry, vital signs, cardiac, and pulmonary status, and give supportive care as necessary. Overdoses must be reported per Section 7.8.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-

specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1.1 Adverse Event List for Niraparib

The current effective version of the Investigator Brochure should be consulted for the most up to date information regarding the safety profile for niraparib.

The following adverse reactions (all CTCAE (version 5.0) 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

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed in the product Reference Safety Information contained in the Investigator Brochure should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

  Of note: GSK will process unlikely related SAE's as related.

7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening/fatal complication treating investigators must immediately notify the Overall PI.

7.3.2 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.4 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

7.7 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.8 Reporting to GSK

7.8.1 Serious Adverse Events

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 AEs (or SAEs, if hospitalization is prolonged due to the AE).

**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.

7.8.2 Adverse Events of Special Interest (AESIs)

Selected non-serious AEs and SAEs are also known as Adverse Events of Special Interest.

Any Serious Adverse Event of Special Interest of scientific and medical concern specific to the study treatment requires ongoing monitoring and rapid communication by the Investigator to the Sponsor Institution and GSK .

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

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

AESI should be collected and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the Sponsor Institution and GSK upon awareness for any patient who has received niraparib (regardless of the timeframe since the last dose)
- Pneumonitis should be reported to the Sponsor Institution and GSK through 90 days after the last dose of study drug
- Embryo-fetal toxicity should be reported as outlined in the Pregnancy reporting section.

7.8.3 Special situations: Abuse, Misuse, Medication Errors Overdose and Accidental or Occupational Exposure

- Abuse: is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.
- Misuse: medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- Medication error: is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

Overdose: is a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. If an overdose occurs with a GSK product, the Sponsor Institution and GSK should be notified immediately, and the patient should be observed closely for AEs. GSK should only receive special situation reports if SAE is associated with drug. Non-serious AE's or special situations without SAE associated, do not need to be reported to GSK on SAE forms within 24 hours. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose, should be reported.

- Accidental /Occupational exposure: is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure associated with a GSK product must be reported on a Special Situations Report Form to the Sponsor Institution within 5 business days of awareness. Of note, GSK Case Processing does not need to receive the Special Situations report form unless a serious AE has occurred in association with a special situation. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with a serious AE, an SAE Report Form must also be submitted to the Sponsor Institution and to GSK within 24 hours of awareness.

7.8.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

- For any AE that is serious, associated with the use of the study treatment, and unexpected (defined as any term not listed in the expectedness section of the current Investigator's Brochure or current prescribing information) additional reporting requirements are described below. These types of reports are referred to as (SUSARs).
- For interventional clinical trials, if the SUSAR is fatal or life-threatening, associated with the use of the study treatment, and unexpected, the Sponsor will report to Regulatory Authorities and Independent Ethics Committees (IECs) within 7 calendar days after the Investigator learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).
- For all other SUSARs, the Sponsor will report to Regulatory Authorities and IECs within 15 calendar days after the Sponsor learns of the event.

The Sponsor will also provide annual safety updates to the Regulatory Authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

In addition, the SUSAR will be distributed to the Investigators/sites, utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and GSK per the governing institutional requirements and in compliance with local laws and guidelines.

Please refer to the current Investigator's Brochure (IB) for a list of expected adverse events following treatment with niraparib.

7.8.5 Assessment of Adverse Events

Each AE will be assessed by the investigator with regard to intensity and causality with regard to study treatment as outlined below.

7.8.6 Severity Assessment

All AEs will be assessed by the Investigator for severity* according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0; National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity grades 1 through 5 provide unique clinical descriptions of severity of each adverse event. The CTCAE v5.0 is available on the NCI/NIH website.

Please note that there is a distinction between **serious** and **severe** AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.1.1. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

7.8.7 Relationship to Study Intervention

The Investigator must provide a causality assessment regarding the relationship of the event with the study drug and/or study procedure for all AEs. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- Related: A causal relationship between the medicinal product and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE, etc. Positive rechallenge/dechallenge is supportive.

- Not Related: A causal relationship between the medicinal product and AE is not a reasonable possibility: there is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

7.8.8 Collection and Recording of Adverse Events

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as, “How have you been feeling since your last study visit?” The Investigator will document the nature of AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All AEs will be collected from the day of the signed informed consent form until 30 days after last dose of study treatment; SAEs and AESIs will be collected and recorded in the eCRF for each patient from the day of signed informed consent until 90 days after the last dose of study drug (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer

therapy). through the and reported accordingly. SAEs considered by the Investigator to be related to study medication are reported throughout the Follow-up Assessment Period.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, or reported by patient), will be collected and recorded in the eCRF for each patient from the day of the signed informed consent form until 30 days after last dose of study treatment

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the Treatment Period. Pre-existing conditions will be recorded as Medical History on any future SAE Report Forms.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.

7.8.9 Follow-Up of Adverse Events

All AEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

7.8.10 Reporting to the Sponsor Institution

All SAEs and AESIs must be reported to the Sponsor Institution within 24 hours of becoming aware of the initial SAE/AESI or any follow-up information regarding the SAE/AESI using the SAE reporting information below. SAEs/AESIs must be reported after study completion, if the SAE/AESI is assessed as study-drug related.

Sponsor Institution SAE, AESI Reporting Information
Email: JCleary@partners.org and KatherineA_Metayer@dfci.harvard.edu Fax: +1-617-582-7988 Telephone: + 1-617-632-5919

7.8.11 Reporting to GSK

The Sponsor Institution must report all SAEs and all follow up information to GSK on an SAE Report Form within 24 hours of becoming aware of the initial event or follow-up information.

The Sponsor Institution must provide a causality assessment and must sign and date all SAE Report Forms.

If supporting documentation is included in the submission to GSK (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), please redact any patient identifiers (including Medical Record number).

GSK SAE, AESI, Pregnancy Reporting Information
Email:OAX37649@gsk.com Fax Number: +44(0) 208754 7822

Pregnancy

The Sponsor Institution has the responsibility to monitor the outcome of all pregnancies reported during the Investigator Sponsored Trial.

The Sponsor Institution must report all pregnancies associated with GSK product including follow up outcomes to GSK within 24 hours of awareness.

Each pregnancy must be reported on an Initial Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. Pregnancy is not an AE, and therefore does not need to be reported as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy on the Pregnancy Outcome Report Form. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form, reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor Institution and GSK within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

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 sponsor-investigator or qualified designee to GSK at gsk-rd.complaints@gsk.com. 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.

8. PHARMACEUTICAL INFORMATION

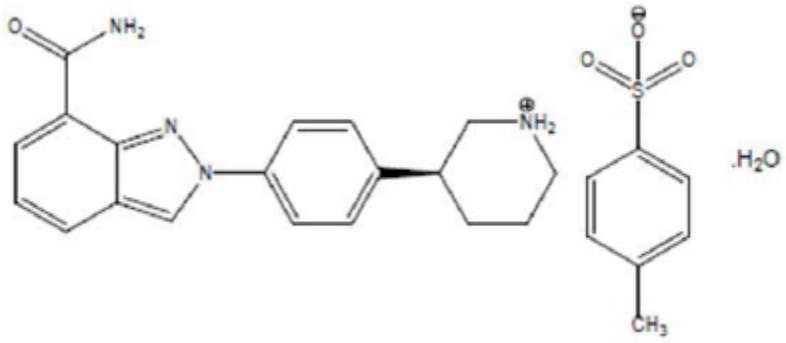
A list of the adverse events and potential risks associated with the investigational administered in this study can be found in **Section 7.1.**

8.1 Niraparib (MK-4827) – capsule containing tartrazine

8.1.1 Description

Chemical Name: [3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]

Chemical Structure:



Molecular formula: $C_{26}H_{30}N_4O_5S$

Molecular Weight: 510.617 daltons

8.1.2 Form

Niraparib drug product is formulated as a dry blend of niraparib tosylate monohydrate and lactose monohydrate lubricated with magnesium stearate. Niraparib will be supplied as 100mg capsules in a 93-count bottle. It is permissible for DF/HCC pharmacy to open stock bottles and dispense the ordered quantity of niraparib in standard amber prescription bottles.

8.1.3 Storage and Stability

Niraparib drug product is packaged in high-density polyethylene (HDPE) bottles with child-resistant plastic closures. The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. Until dispensed to the patients, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

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.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to

themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.5 Availability

Niraparib is an investigational agent that will be supplied by GSK, Inc.

8.1.6 Administration

Participants will take niraparib at the recommended phase two dose of 200 or 300 mg by mouth once daily. Niraparib can be taken with or without food. Doses of niraparib should be taken approximately 24 hours apart. Doses that would be outside of this time range should be considered missed and should not be taken. Vomited doses should not be retaken. Niraparib capsules should be swallowed whole and should not be chewed, crushed, opened, or dissolved.

8.1.7 Ordering

Niraparib will be ordered from GSK by site pharmacy personnel.

8.1.8 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

8.1.9 Destruction and Return

Expired and returned supplies of niraparib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. At the end of the study, unused supplies of niraparib should also be destroyed according to institutional policies and destruction will be documented in the Drug Accountability Record Form.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Archival Tumor Tissue Collection

9.1.1 Collection of Archival Tumor Specimens

Patients who have not previously had their tumor genomically characterized will undergo baseline collection of archival tissue to verify eligibility status. Participants who have previously had sufficient molecular analysis for identification of the genomic requirements for eligibility are not required to repeat testing prior to enrollment (e.g. OncoPanel or other Next Generation Sequencing [NGS] analyses, germline *BRCA*

testing, etc.).

9.1.2 Handling of Archival Tumor Specimens

Archival specimens should be labeled with the DFCI protocol number and study subject number. A total of 10 unstained slides should be delivered to the coordinating site for performance of NGS testing at:

Lauren Brais
Dana-Farber Cancer Institute
450 Brookline Avenue, DA1220
Boston, MA 02215
Phone: 617-632-6758

9.2 Fresh Tumor Tissue Collection

9.2.1 Collection of Biopsy Specimens

Mandatory fresh tumor biopsies will be obtained from participants at baseline (any time following informed consent and prior to the first dose of study medication). An optional fresh tumor biopsy at the time of disease progression will be offered to participants who derived clinical benefit on trial. Whenever possible, the time of progression biopsy should be obtained prior to the initiation of another cancer treatment. In the event this is not feasible, the time of progression biopsy can be obtained up to 8 weeks after the last dose of niraparib.

9.2.2 Handling of Biopsy Specimens

Core biopsy samples should be obtained for analysis. Three to four biopsy passes utilizing a 16-18-gauge needle is preferable, but a 20-gauge core needle biopsy is also acceptable at the discretion of the interventionalist performing the procedure. Collection of less than the goal amount of tissue will not be considered a protocol violation and should be based upon the clinical judgment of the clinician performing the biopsy procedure.

Biopsy tissue should be processed with the first core formalin fixed and paraffin embedded (FFPE) per routine local procedures and the subsequent three cores should be processed into OCT blocks. Processing information provided in Appendix D

9.2.3 Shipping of Biopsy Specimens

Biopsy samples should be shipped to the coordinating site as soon as possible. The coordinating site will batch ship samples to the Broad Institute Center for Cancer Precision Medicine.

Biopsy samples should be sent to DFCI at:

Lauren Brais
Dana-Farber Cancer Institute
450 Brookline Avenue, DA1220
Boston, MA 02215
Phone: 617-632-6758

9.2.4 Prioritization of Specimens

In the event that tissue samples are limited; the highest priority will be sending the limited tissue sample for WES. The functional HR assay will be second on the priority list. Finally, sample for organoid generation will be third on the priority list.

9.3 Germline Blood Sample Collection

9.3.1 Collection of Germline Specimens

A germline blood sample will be collected once for all patients any time following consent, preferably at baseline to be paired with the pre-treatment fresh tumor biopsy obtained for WES.

9.3.2 Handling of Germline Specimens

The blood sample should be labeled with the protocol number, study subject number, and the date of collection.

- One 10 mL sample will be drawn into an EDTA containing test tube.
  <u>If possible</u>:
  - Whole blood sample should be aliquoted into three 5 mL cryovials using a 10 mL pipette. Be sure to invert the EDTA tube prior to aliquoting to ensure homogenous samples (as some settling can occur).
  - Aliquot 3.5 mL of whole blood into the first two cryovials and the remaining whole blood into the last 5 mL cryovial.
- Freeze immediately upright at -80ºC until shipping.

At DFCI, samples will be managed by the GI Translational Laboratory. Other sites should manage samples according to their institutional standard procedures. **All samples should be stored at -80ºC until shipment is requested by the coordinating site.**

9.3.3 Shipping of Germline Specimens

When requested, the germline blood samples will be sent to the coordinating site. The coordinating site will batch ship samples to the Broad Institute Center for Cancer Precision Medicine.

Germline samples should be sent on dry ice to DFCI at:

Lauren Brais
Dana-Farber Cancer Institute
450 Brookline Avenue, DA1220
Boston, MA 02215
Phone: 617-632-6758

9.4 Plasma Collection for cfDNA

9.4.1 Collection of Specimens

Samples are to be collected any time prior to dosing on Days 1, 8, 15 and 22 of Cycle 1, and on Day 1 of each subsequent cycle, and at the off-study visit.

9.4.2 Handling of Specimens

1. Draw two 10 mL blood samples into EDTA-containing tubes or Streck Tubes.
2. Blood samples should be labeled with: cfDNA, protocol number, study subject number, and the date of the draw.
3. cfDNA samples should be processed as follows:
    1. Wait at least 30 minutes to process the blood sample and blood must be processed within 2 hours of collection
    2. Centrifuge for 15 minutes at 1650 (+\- 150) x g. Record blood collection and sample processing times. (NOTE: Brake switch must be off so the cell/plasma interface is not disturbed.)
    3. Using a 5 ml pipette, aliquot 1 ml of the clear yellow plasma layer supernatant into eight 2 ml cryovials (Nunc CryoTube - Thermo Scientific™ 368632), taking care to avoid pipetting liquid near the RBC/plasma interface. Record volume of all samples.
    4. Label the samples using the following general labeling structure: [Protocol #18-207].[Timepoint (Baseline, Cycle #, or discontinuation)].[Type of Sample].[Patient Number] – [Aliquot Number]. (For example: the first aliquot of the baseline sample would be “Protocol 18-207.Baseline.plasma.p1-1.”
    5. Freeze immediately upright at -80ºC or colder until shipping.

At DFCI, samples will be managed by the GI Translational Laboratory. Other sites should manage samples according to their institutional standard procedures. **All samples should be stored at -80ºC until shipment is requested by the coordinating site.**

9.4.3 Shipping of Specimens

When requested by the coordinating site, the plasma samples will be sent to the coordinating site. The coordinating site will batch ship samples to the Broad Institute Center for Cancer Precision Medicine.

Plasma samples should be shipped on dry ice to DFCI at:

Lauren Brais
Dana-Farber Cancer Institute
450 Brookline Avenue, DA1220
Boston, MA 02215
Phone: 617-632-6758

9.5 Circulating Tumor Cell Collection

Circulating Tumor Cells subpopulations (mesenchymal and epithelial) will be enumerated directly from whole blood according the protocol in Witek et. al..[22] CTC will be enumerated on the first day of each treatment cycle, on the day of imaging (CT or MRI) scan, EOT.
Genomic DNA from CTC will be extracted, and mutational analysis performed (NGS) and compared with primary/metastatic tumor tissue. Genomic testing from CTC to be done by KUMC labs (Dr. Witek).

Whole blood for CTC analysis will be collected into one lavender (EDTA) top Vacutainer® tube per test, until the vacuum is exhausted. Then, gently invert tubes 10 times to ensure mixing of anti-coagulant in tubes with EDTA as the anticoagulant and stored at room temperature. Blood will be available for testing within 3-5 h post collection.
These blood draws will be separate blood draws.

This blood to be sent ambient within 3 – 5 hours post-collection, directly to the analysis lab and NOT stored for banking (analyses to be done 'real time').

If the blood samples cannot be delivered within 4h for CTC analysis, please use the following protocol to stabilize the blood:

- Dr. Soper group will provide stabilizing buffer for the blood.

  Add 400 µL of the stabilizing buffer to the blood in the EDTA tube before shipment.
- Sample should be shipped on ice (cold) to the lab at KU-lab and received within 24-72h (the address is listed below).

  Prof. Soper Research Lab
  The University of Kansas
  Integrated Science Building

  1567 Irvingville Road
  Lawrence, KS 66045
  mobile# 225-803-5627

10. STUDY CALENDAR

Baseline assessments are to be conducted within 14 days prior to start of protocol therapy, with the exception of the baseline imaging which may be obtained within 28 days of the start of protocol therapy and serum pregnancy test which must occur within 7 days of protocol therapy. Assessments must be performed prior to administration of any study agent.

Table 1: Study Calendar

	Pre-Study	Cycle 1 Day 1	Cycle 1 Day 8[J]	Cycle 1 Day 15[J]	Cycle 1 Day 22[J]	Cycle 2+ Day 1[K]	Off Treatment[L]	Every 3 Months After Discontinuation[M]
Informed consent	X							
Demographics	X							
Medical history	X							
Physical exam	X	X	X	X	X	X	X	
Vital signs[A]	X	X	X	X	X	X	X	
Height	X							
Weight	X	X	X	X	X	X	X	
Performance status	X	X	X			X	X	
CBC w/diff, plts[B]	X	X	X	X	X	X	X	
Serum chemistry[C]	X	X	X	X	X	X	X	
Adverse event evaluation	X	X	X	X	X	X	X	
Assess for MDS/AML	X	X----------X[D]						
Radiologic evaluation	X	CT or MRI imaging of any disease-involved site. Imaging to be conducted every 8 weeks (± 1 week scheduling window).[O]						
Serum β-HCG[E]	X	X----------X[E]						
Fresh Tumor Tissue Biopsy, Germline Blood Sample[F]	X						X[F]	
Archival Tissue Collection[G]	X							
cfDNA[H]		X	X	X	X	X	X	
Bone Marrow Aspirate and biopsy[N]		X----------X					X	X
Niraparib[I]		X----------X						
Telephone or care provider contact								X

A. Vital signs to include heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation (O_2 sat). BP/HR should be monitored at least weekly for the first two months, and then monthly for the first year and periodically thereafter during niraparib treatment.

B. CBC with diff and plts to be performed weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically thereafter. Additional time points may be required as detailed in **Section 6.3**.

C. Sodium, potassium, chloride, CO_2, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase,

total bilirubin, SGOT [AST], SGPT [ALT], globulin, lactate dehydrogenase (LDH), direct bilirubin, calcium, uric acid, phosphorus, gamma-glutamyl transferase (GGT).

D. Patients will be followed for 5 years for MDS/AML
E. Serum pregnancy test to be collected in women of childbearing potential within ≤3 days prior to initiating protocol therapy, every 3 cycles (i.e. C4D1, C7D1) and at the off-treatment evaluation (a urine pregnancy test is also acceptable if preferred per updated standard requirements). Childbearing potential defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months; or women with a documented plasma follicle-stimulating hormone level >35µlU/mL). Of note: GSK recommends monthly pregnancy testing.
F. Mandatory fresh tumor tissue biopsy and germline blood sample required pre-treatment as detailed in **Section 9.2**. An additional optional biopsy at the time of disease progression to be offered to participants as described in **Section 9.2**. Germline sample will be collected once and may be collected anytime following consent, preferably at baseline.
G. Collection of archival tissue required only in patients who need testing for eligibility purposes as detailed in **Section 9.1**.
H. cfDNA to be collected any time pre-dose on Days 1, 8, 15 and 22 of Cycle 1, on Day 1 of each subsequent cycle, and any time during the Off Study visit as detailed in **Section 9.4**.
I. Niraparib administration as described in **Section 5.3**. Adequate supply should be dispensed to participants to accommodate any pre-planned scheduling delays.
J. A ± 3 day scheduling window exists to accommodate adverse weather, holidays, vacations, or any other clinic scheduling issues.
K. A ± 1 week scheduling window exists to accommodate adverse weather, holidays, vacations, or any other clinic scheduling issues.
L. Off-treatment evaluation. Note: for IND trials, follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of study treatment.
M. Participants will be followed until death or withdrawal of consent after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3 months (±1 month window). Participants should be followed for survival status as well as for assessment of new primary malignancies.
N. For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria) and other sample testing results related to MDS/AML
O. After two years of being on treatment, the frequency of restaging scans can be reduced to every 3-4 months (every 12-16 weeks +/- 1 week scheduling window) at the investigator’s discretion.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks (+/- 1 week). In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response. After two years of being on treatment, the frequency of restaging scans can be reduced to every 3-4 months (every 12-16 weeks +/- 1 week scheduling window) at the investigator's discretion.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

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

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

11.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless there has been demonstrated growth of the lesion following the completion of radiation.

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



Non-measurable 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), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based

evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

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

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

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

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent

fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

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

MIBG (meta-iodobenzylguanidine). The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

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

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

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.3.1 Evaluation of Target Lesions

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

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

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

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

11.1.3.2 Evaluation of Non-Target Lesions

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

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

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

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

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

11.1.3.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.3.4 Evaluation of Best Overall Response

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

Table 2: For Participants with Measurable Disease (*i.e.*, Target Disease)				
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Table 3: For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.4 Duration of Response

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

death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

11.1.5 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.6 Response Review

Evaluation of scans will be done centrally at the DFCI using the Tumor Metrics Core.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in **Section 7.0** (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a proof of concept phase 2 clinical trial designed to test the hypothesis that advanced pancreatic cancers with a deficiency in DNA HR repair will respond to niraparib. This single arm trial will enroll a maximum of 32 pancreatic adenocarcinoma patients who will receive niraparib at the recommended phase 2 dose.

The trial has a two stage Minimax design[23]. Eighteen patients will be enrolled in the first stage. If one or more patients have progression-free survival of at least six months, 14 additional patients will be enrolled. If none of the first 18 patients have progression-free survival of 6 months or more, the study will close for lack of efficacy. The probability of early termination is 0.39.

The primary objective is the evaluation of 6 month progression-free survival rate. With 32 subjects, the study has at least 80% power and a one-sided 0.1 significance level to differentiate between an unacceptable 6 month progression-free survival rate of 5% and a desirable 6 month progression-free survival rate of 17%. Observing at least 4 patients with progression-free survival of at least 6 months will be sufficient for the overall rejection of the null hypothesis in favor of the desirable 6 month progression-free survival rate of 17%.

Progression-free survival is defined as the time from registration to documented disease progression or death from any cause, whichever occurs first. Subjects who have not experienced an event of interest by the time of analysis will be censored at the date of the last disease assessment without progression.

Secondary objectives include the determination of the overall response rate per RECIST criteria and overall survival rates. Overall survival is defined as the time from registration to death from any cause, and subjects who are thought to be alive at the time of final analysis will be censored at the last date of contact.

The safety of niraparib will be followed and toxicities will be reported using CTCAE v.5.0 criteria.

Time-to-event distributions will be estimated using the Kaplan-Meier method. Comparisons of subgroups will be made using the log rank test and Cox modeling. Response and toxicity rates will be compared between subgroups using Fisher's exact tests; multivariable logistic regression modeling will be used to adjust for the effect of any covariates that are associated with these categorical outcomes.

This trial will test several biomarkers for their ability to predict responses to niraparib. We will utilize logistic regression for each biomarker and adjust the p-value for multiple comparisons using the false discovery rate method.

13.2 Sample Size, Accrual Rate and Study Duration

The planned sample size is a maximum of 32 subjects. The planned accrual rate is approximately 4 patients per quarter. Up to an additional year of follow-up will be required on the last participant accrued to observe the patient's response and survival following study therapy, for a total study length of approximately three years.

13.3 Reporting and Exclusions

13.3.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of study medication.

13.3.2 Evaluation of the Primary Efficacy Endpoint

All eligible participants included in the study who receive at least one dose of study medication will be assessed for response, even if there are major protocol therapy deviations. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

14. PUBLICATION PLAN

The results should be made public within 12 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three

(3) years after the end of the study.

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15. APPENDIX A PERFORMANCE STATUS CRITERA

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

16. APPENDIX B SAE REPORTING FORM

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Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number

SERIOUS ADVERSE EVENT (SAE)

Did the subject experience a serious adverse event during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

SECTION 1

Event	Start Date	Start Time	Outcome	End date	End Time	Maximum Intensity	Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the SAE	With-drawal	Date site was made aware of the SAE	Time site was made aware of the SAE	Relationship to Study Treatment(s)
Diagnosis Only (*if known*) Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae 5=Fatal	*If fatal, record date of death.* Day Month Year	Hr : Min 00:00-23:59	1=Mild 2=Moderate 3=Severe X=Not applicable	1=Study Treatment(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted/ Delayed X=Not applicable	Did the subject withdraw from study as a result of this SAE? Y=Yes[1] N=No	Day Month Year	Hr : Min 00:00-23:59	Is there a reasonable possibility the SAE may have been caused by the study treatment? Y=Yes N=No
e.g., Anaphylaxis	*25 JAN 18*	*13:25*	*1*	*27 JAN 18*	*10:20*	*1*	*4*	*Y*	*30 JAN 18*	*13:25*	*Y*
		:			:					:	
		:			:					:	

[1] *Complete Study Conclusion page and ✓Adverse event as reason for withdrawal.*

SECTION 2 Seriousness *(specify reason(s) for considering this a SAE, ✓all that apply:*

[A] ☐ Results in death
[B] ☐ Is life-threatening
[C] ☐ Requires hospitalisation or prolongation of existing hospitalisation
[D] ☐ Results in disability/incapacity
[E] ☐ Congenital anomaly/birth defect
[F] ☐ Other, *specify* _____ *(see definition of SAE)*
[G] ☐ Possible drug-induced liver injury (see definition in SAE section of the protocol)

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Protocol Identifier	Subject Identifier

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 3 Demography Data

For GSK use only
Enter the subject's year of birth.

Year of birth ☐☐☐☐ Year

Imputed date of birth 3 0 J U N ☐☐☐☐ Day Month Year

Sex ☐ Male ☐ Female Weight ☐☐☐.☐ kg Height ☐☐☐ cm

SECTION 4 If Study Treatment(s) was Stopped, Did the Reported Event(s) Recur After Further Study Treatment(s) were Administered?

☐ Yes ☐ No ☐ Unknown at this time ☐ Not applicable

SECTION 5 Possible Causes of SAE Other Than Study Treatment(s), *✓all that apply:*

☐ Disease under study
☐ Medical condition(s) *specify* _____
☐ Lack of efficacy
☐ Withdrawal of study treatment(s)
☐ Concomitant medication(s) *specify* _____
☐ Activity related to study participation *(e.g., procedures)*
☐ Other, *specify* _____

SECTION 6 RELEVANT Medical Conditions

Specify any RELEVANT past or current medical disorders, allergies, surgeries that can help explain the SAE. Ensure each medical condition recorded in this section is also recorded in the appropriate Medical Conditions form.	Date of Onset Day Month Year	Condition Present at Time of the SAE? Y= Yes N=No	*If No, Date of Last Occurrence* Day Month Year

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Protocol Identifier	Subject Identifier	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 7 Other RELEVANT Risk Factors *Provide any family history or social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE). Ensure each risk factor recorded in this section is also recorded in the appropriate Medical Conditions form.*

SECTION 8 RELEVANT Concomitant Medications *Include details of any concomitant medication(s) that may help explain the SAE, may have caused the SAE or was used to treat the SAE. Ensure each concomitant medication recorded in this section is also recorded in the Concomitant Medication form.*

Drug Name (Trade Name preferred)	Dose	Unit	Frequency	Route	Taken Prior to Study? Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Medication? Y=Yes N=No	Reason for Medication
e.g., Zantac	*150*	*mg*	*BID*	*PO*	*N*	*25 JAN 18*	*27 JAN 18*	*N*	*Gastric ulcer*

SECTION 9 Details of Study Treatment(s)

Was treatment blind broken at investigational site? ☐ Yes ☐ No ☐ Not applicable

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Protocol Identifier	Subject Identifier	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 10 Details of RELEVANT Assessments *Provide details of any tests or procedures carried out to diagnose or confirm the SAE (e.g., laboratory data with units and normal range) if data for this SAE have not been previously entered, and the CRF includes a page for the test, ensure the data is also entered on the page.*

SECTION 11 Narrative Remarks *(provide a brief narrative description of the SAE and details of treatment given)*

Investigator's signature _____
(confirming that the data on the SAE pages are accurate and complete)

Date ☐☐ Day ☐☐☐ Month ☐☐ Year

Investigator's name (print) _____

Internet Link for Form FDA 3500A (Mandatory Reporting Form for investigational agents): http://www.fda.gov/medwatch/getforms.htm

17. Appendix C Pregnancy Reporting Form

TESARO	**Initial Pregnancy Form**
Program Drug Name:	Protocol Number:

	☐ Unknown ☐ Other:
Lactation Exposure Details	Age of baby at the time of the potential exposure _____ Length of potential exposure (timeframe)_____

Narrative:

Treating Physician:		
Printed Name of Treating Physician:	**Signature of Treating Physician:**	**Date (DD/MMM/YYYY):**

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Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number

PREGNANCY NOTIFICATION FORM

This form should be completed according to the protocol reporting requirements.
Note: Most protocols do not require collection of subject's partner pregnancy.
Complete this form for each subject or subject's partner who becomes pregnant during the study period. Send a copy of the form to GlaxoSmithKline (GSK will provide separately a list of contact names and information) by mail or fax (e-mail preferred) within 24 hours of learning of the pregnancy. Once form has been completed please email to mailbox: OAX37649@GSK.com (or fax +44(0)20 8754 7822).

Who is this form being completed for, ✓*one:*
☐ Subject
☐ Subject's partner

MOTHER'S RELEVANT MEDICAL/FAMILY HISTORY

Mother's year of birth ☐☐☐☐ Year

Date of last menstrual period ☐☐ Day ☐☐☐ Month ☐☐ Year

Estimated date of delivery ☐☐ Day ☐☐☐ Month ☐☐ Year

Was the mother using a method of contraception? ☐ Yes ☐ No

If Yes, specify: _____

Type of conception, ✓*one:*
☐ Normal (includes use of fertility drugs)
☐ IVF (in vitro fertilisation)

Relevant laboratory tests and procedures (e.g., ultrasound, amniocentesis and chorionic villi sampling, including dates of tests and procedures).

_____

_____

Number of previous pregnancies ☐☐ Pre-term ☐☐ Full-term

If applicable, record the number in the appropriate categories below:

☐☐ Normal births
☐☐ Stillbirths
☐☐ Children born with defects
☐☐ Spontaneous abortion
☐☐ Elective abortion
☐☐ Other

Record details of children born with defects: _____

Are there any additional factors that may have an impact on the outcome of this pregnancy? ☐ Yes ☐ No

If Yes, specify: _____

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Protocol Identifier	Subject Identifier	Centre Number	

PREGNANCY NOTIFICATION FORM (Continued)

FATHER'S RELEVANT MEDICAL/FAMILY HISTORY

Only recorded if required by the protocol and Informed Consent of the father has been obtained.

(Include habitual exposures such as alcohol/substance abuse, chronic illnesses, familial birth defects/genetic/ chromosomal disorders and medication use)

_____

_____

DRUG EXPOSURES

*In the following table, list all medications (including study medications) the subject received during the study period (e.g. prescription, OTC, vaccines, recreational, alcohol, etc.). **Enter the investigational product details on the first line** (if the investigational product is blinded, enter 'Investigational Product' on this line). If there are extensive concomitant medications, attach a copy of the Concomitant Medications CRF page.*

Drug Name (*Trade Name preferred*)	Route of Admin. or For-mulation	Total Daily Dose	Units	Started Pre-Study Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Med-ication Y=Yes N=No	Reason for Medication

Was the subject withdrawn from the study as a result of this pregnancy? ☐ Yes ☐ No

REPORTING INVESTIGATOR INFORMATION (Forward to a more appropriate physician if needed)

Name _____ Title __ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____

Investigator's signature _____ Date ☐☐ Day ☐☐☐ Month ☐☐ Year
(confirming that the data on these pages are accurate and complete)

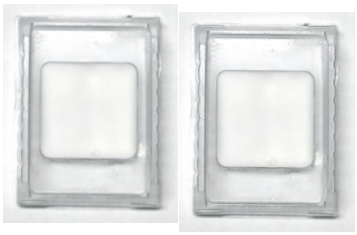
Investigator's name (print) _____

18. APPENDIX D COLLECTION OF TUMOR FOR CORRELATIVE STUDY

Participants will have tumor tissue collected as described in Protocol Section 2. A total of 2-4 core biopsy samples should be collected at each biopsy time point.

All samples must be labeled with the DF/HCC protocol number, study subject number, and date of sample collection. Use labels that will not smear or fall off under cold or moist conditions.

Table 18. Biopsy tissue specimen samples to be collected.

Tumor FFPE block	**OCT embedded Tumor**
	
Core 1 FFPE Block	Core 2, 3, and 4+

18.1 For the pre-treatment biopsy tissue should be collected in the following priority:

18.1.1 One core should be formalin-fixed and paraffin-embedded (FFPE) per routine local procedures.

18.1.2 Three core should be frozen in OCT:

- A plastic cryomold will be labeled with the patient identifier and date of procedure. OCT compound will be placed into the cryomold at the time of the biopsy initiation, the OCT cryomold should be filled 1/3 with OCT to prepare for the sample. The cryomold should then be placed upon dry ice.
- The tissue sample will be placed into the OCT cryomold and additional OCT will be added to fill the cryomold.
- The cryomold must then immediately be placed upon dry ice.
- The specimen will be stored at -80˚C until shipment.
- A separate cryomold should be used for each individual core sample.

18.1.3 Three will be placed in OCT and all remaining cores should be frozen in OCT per instructions in priority #2.

18.2 For the progression biopsy tissue should be collected in the following priority:

18.2.1 One core should be formalin-fixed and paraffin-embedded (FFPE) per routine local procedures.

18.2.2 One core should be frozen in OCT for WTS:

- A plastic cryomold should be labeled and several drops of OCT compound will be placed into the cryomold at the time of the biopsy.
- The tissue sample will be placed into the OCT and covered with additional drops of OCT.
- The cryomold must then immediately be placed upon dry ice.
- The specimen will be stored at -80˚C until shipment.
- A separate cryomold should be used for each individual core sample.

18.2.3 (If available) All remaining cores should be frozen in OCT per instructions in priority #2.

18.2.4 Organoid Development Also refer to Protocol Section 2. Tissue for organoid development will be collected on all participants pre-treatment and optionally at the time of progression.

18.3 Sample Collection and Shipping Instructions:

18.4 All samples must be labeled with the DF/HCC protocol number, study subject number, and date of collection. Use labels that will not smear or fall off under cold or moist conditions.

18.5 A total of one (minimum – goal: three) core biopsy samples will be collected at each biopsy time point.

18.6 Samples must be frozen in OCT as described in **Section 18.2.2** above.

18.7 Samples must be shipped within 72 hours of the biopsy procedure.

18.8 Samples should be placed in a primary receptacle (e.g. insulated cooler/Styrofoam container), then into a secondary receptacle (e.g. sturdy cardboard box). These primary and secondary containers are available commercially as combination packaging. The package contents are placed in this order:

18.9 Wrap the samples in enough absorbent material to absorb at least three times the contents should leakage occur.

18.10 Place the wrapped samples in a plastic bag and seal (heat seal or zip lock)

18.11 Place the sealed bag in the bottom of the primary receptacle.

18.12 Add Styrofoam peanuts or equivalent (barrier to dry ice and shock stabilizer)

18.13 Add a sheet of cardboard onto the top of the primary receptacle.

18.14 Adequate dry ice should be included in the container to last the duration of the journey (i.e. 24 hours).

18.15 If there is room remaining, add filler material to avoid content movement during transport.

18.16 The primary container should be taped shut and then placed in the secondary cardboard container.

18.17 Complete a sample inventory form. A copy of an example form is in **Section 19.**

Appendix E – Specimen Inventory Form. If possible, also send this electronically via email.

18.18 Seal the sample inventory form(s) into a protected plastic bag (zip lock).

18.19 Place the plastic bag containing the sample inventory form(s) on top of the secured primary container lid (insulted cooler/Styrofoam container) so that it is immediately accessible upon opening the cardboard box.

18.20 Tape the shipping box securely closed. Use tape that is resistant to moisture and cold.

18.21 Label the box exterior in accordance with the applicable DOT CFR / IATA Regulations.

18.22 Complete a shipping label and attach it to the outside of the box.

18.23 Advanced notice of incoming shipments must be given to:

18.24 Lauren Brais (LaurenK_Brais@DFCI.HARVARD.EDU; 617-632-6758)

18.25 Notice should be given at least 1 business day in advance of sample shipment whenever possible.

18.26 **Samples must be shipped via tracked expedited overnight shipping (e.g. FedEx, UPS) and must be shipped to arrive the following business morning (i.e. must arrive Monday – Friday morning). Samples <u>cannot</u> be shipped to arrive on weekends or federal holidays.**

18.27 Shipping Address:
Lauren Brais
Dana-Farber Cancer Institute
450 Brookline Avenue, DA1220
Boston, MA 02215
Phone: 617-632-6758

18.28 Questions may be directed to:

18.29 Lauren Brais (LaurenK_Brais@DFCI.HARVARD.EDU; 617-632-6758)

19. Appendix E – Specimen Inventory Form

Specimen Inventory Form – Wolpin Laboratory Tissue

Please submit an electronic copy of the inventory via email to Lauren Brais (LaurenK_Brais@DFCI.HARVARD.EDU)as well as a hard copy with sample delivery. Retain a copy for study records.

Study Title: Phase 2 Proof-of-Concept Trial Testing the PARP Inhibitor Niraparib in Patients with Pancreatic Cancer Harboring Deficiencies in Homologous Recombination DNA Repair
DF/HCC Protocol Number: 18-207
Overall Principal Investigator: James Cleary, MD, PhD

Subject #	Subject Initials	Date of Collection	Biopsy Site	Block or # of Slides Shipped

Study Contact:
Email:
Phone: