THE UNIVERSITY OF KANSAS
CANCER CENTER

**Investigator Initiated Trial**

**IIT-2017-NIRA-PANC**

# Niraparib in metastatic pancreatic cancer after previous chemotherapy (NIRA-PANC): a phase 2 trial


**SPONSOR - INVESTIGATOR**

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| | |
|---|---|
| **Protocol Number:** | **IIT-2017-NIRA-PANC** |
| **Study Drug(s):** | Niraparib |
| **IND** | 137456 - Exempt |
| **Initial Version:** | Protocol Version 2.0 dated 01-10-2019 |
| **Amendments To Be Decided** | |

## LIST OF COLLABORATORS

**COLLABORATORS**

Andrew Godwin, PhD - Biospecimen Repository Core Facility (BRCF)
Prabhakar Chalise, PhD - Biostatistician
Steven A. Soper, PhD – Biomedical Engineering (Liquid Biopsy Core Facility)
Maggie W. Witek, PhD – Biomedical Engineering (Liquid Biopsy Core Facility)
Say Tang-Rainwater, BASc - Charles River Laboratories, Inc. (Pharmacokinetics Analyses)

## STATEMENT OF COMPLIANCE / PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Sponsor - Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: IIT-2017-NIRA-PANC

Protocol Title: Niraparib in advanced pancreatic cancer after previous chemotherapy (NIRA-PANC): a phase 2 trial

Protocol Version and Date: Protocol Version 2.0 dated 01-10-2018

Sponsor - Investigator Signature _____ _____

Print Name and Title: **Anup Kasi, MD** Date

Site Number: 001

Site Name: The University of Kansas Cancer Center

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# 1 TABLE OF CONTENTS

## 2 LIST OF ABBREVIATIONS

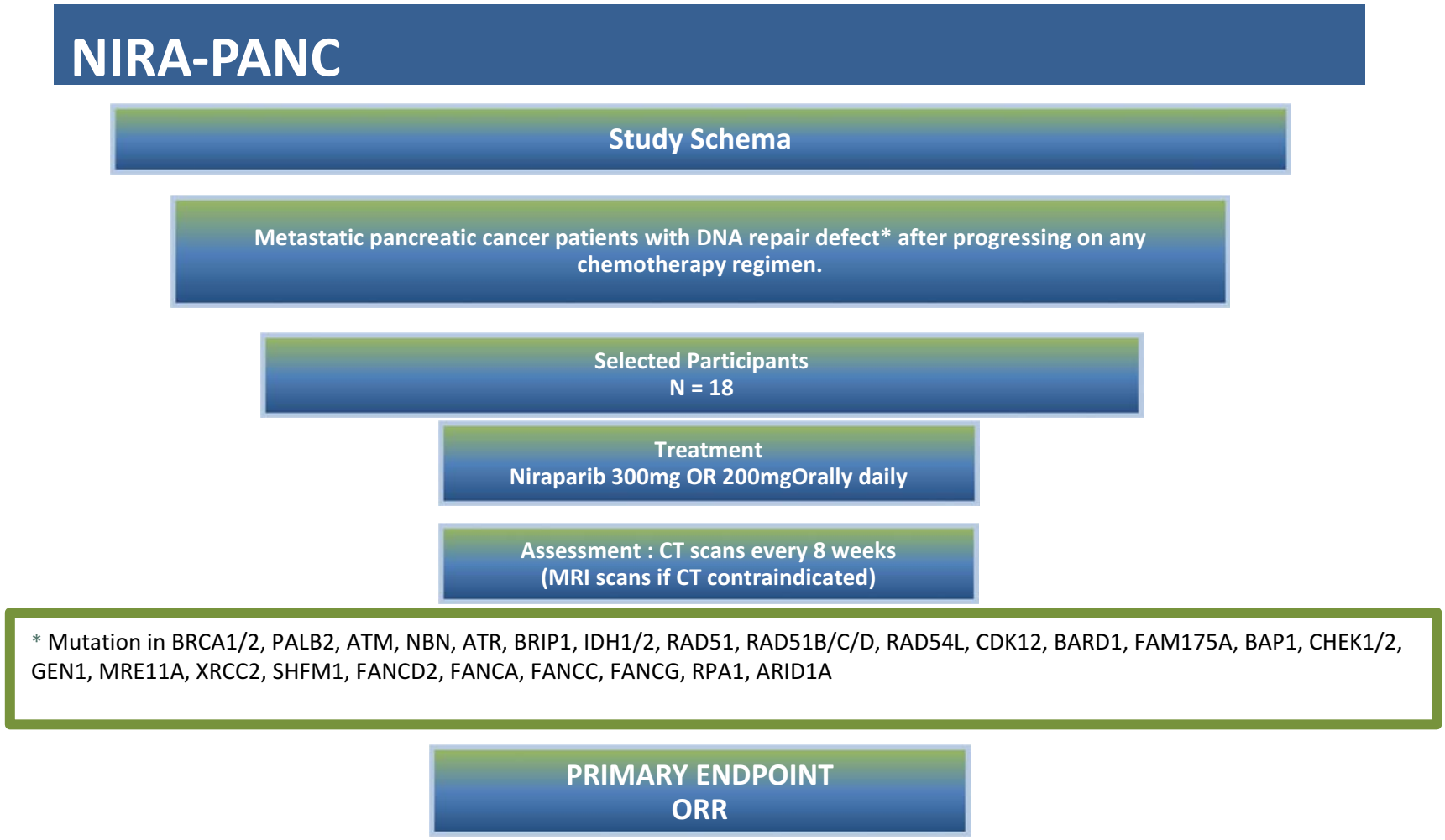
| | |
|---|---|
| 5-FU | Fluorouracil |
| ADME | Absorption, Distribution, Metabolism, And Elimination |
| ADP | Adenosine Diphosphate |
| ADP-ribose | Adenosine Diphosphate-Ribose |
| AE | Adverse event |
| AESI | Adverse Event of Special Interest (TESARO nomenclature = SAE) |
| Aka | Also Known As |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AML | Acute Myeloid Leukemia |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate Aminotransferase |
| ATM | Ataxia-Telangiectasia Mutated |
| ATR | Ataxia-Telangiectasia And Rad3-Related |
| BER | Base excision repair |
| BM | Bone marrow |
| BP | Blood pressure |
| BRCA 1 | Breast cancer gene 1 |
| BRCA 2 | Breast cancer gene 2 |
| BRCAwt | BRCA wild type |
| BRCF | Biospecimen Repository Core Facility |
| BROCA | A genetic mutations cancer test panel (named for Paul Broca) |
| BSEP | Bile Salt Export Pump |
| BUN | Blood urea nitrogen |
| C/A/P | Chest / Abdomen / Pelvis |
| C1D28 | Cycle 1 Day 28 |
| C2D1 | Cycle 2 Day 1 |
| CA 19-9 | Carbohydrate antigen 19-9, also called cancer antigen 19-9 |
| Ca | Calcium |
| CBC | Complete blood count |
| CE | Carboxylesterase |
| CEA | Carcinoembryonic antigen |
| CFI | Chemotherapy-free Interval |
| CFR | Code of Federal Regulations |
| Chk1 | Checkpoint-Like Kinase 1 |
| Chk2 | Checkpoint-Like Kinase 2 |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Science |
| Cl | Chloride |
| CMOL | Clinical Molecular Oncology Laboratory |
| CMP | Comprehensive Metabolic Panel |
| CMV | Cytomegalovirus |
| CNS | Central Nervous System |
| $CO_2$ | Carbon dioxide |
| COX | Cyclooxygenase |
| CR | Complete response |

| | |
|---|---|
| Cr | Creatinine |
| CRC | Clinical Research Center |
| CRF | Case Report Form |
| CRP | C-reactive Protein |
| CSF | Cerebro-Spinal Fluid |
| CT | Computed Tomography |
| CTC | Circulating tumor cell |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTO | Clinical Trials Office |
| CYP | Cytochrome P (an oxidative enzyme) – also CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C12, CYP2C19, CYP2D6, or CYP3A4/5 |
| DFS | Disease-Free Survival |
| DLT | Dose-limiting toxicity |
| DNA | Deoxyribonucleic acid |
| DR | Duration of Response |
| DSB | DNA double-strand breaks |
| DSMB | Data and Safety Monitoring Board |
| DSMC | Data and Safety Monitoring Committee |
| ECG | Electrocardiogram |
| EOT | End of Treatment |
| EQ | European Quality of Life Scale |
| ERCC1 | excision repair cross-complementation group 1 |
| FACT | Functional Assessment of Cancer Therapy |
| FANCC | Fanconi Anemia Group C |
| FANCG | Fanconi Anemia Group G |
| FDA | Food and Drug Administration |
| FOLFIRI | fluorouracil+irinotecan |
| FOLFIRINOX | folinic acid+fluorouracil+irinotecan+oxaliplatin |
| FOLFOX | fluorouracil+oxaliplatin |
| FOSI | Ovarian Symptom Index |
| gBRCAmut | Germline BRCA mutation |
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| GTP | Good tissue practice |
| GU | Genito-Urinary |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | Hazard Ratio |
| HRD | Homologous Recombination Deficiency |
| HRDneg | HRD negative |
| HRPP | Human Research Protections Program |
| HSC | Human Subjects Committee (aka IRB at University of Kansas Medical Center) |
| IB | Investigator's Brochure |
| ICH E6 | International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance |
| ICH | International Committee on Harmonization |
| IIT | Investigator-Initiated Trial |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |

| | |
|---|---|
| IV | Intra-Venous |
| K | Potassium |
| KUCC / KUMC | The University of Kansas Cancer Center / The University of Kansas Medical Center |
| KUCC | The University of Kansas Cancer Center |
| KUMC | The University of Kansas Medical Center |
| LDH | Lactate Dehydrogenase |
| LPS | Lipopolysaccharide |
| MD | Medical Doctor |
| MDS | Myelodysplastic Syndrome |
| Mg | Magnesium |
| mg | Milligram |
| MLH1 | DNA mismatch repair genes |
| mOS | Median Overall Survival |
| mPFS | Median Progression Free Survival |
| MRE11 | DNA-repair protein |
| MRI | Magnetic Resonance Imaging |
| mRNA | Messenger Ribonucleic Acid |
| MSH2 | DNA mismatch repair gene |
| MSH6 | DNA mismatch repair gene |
| Na | Sodium |
| NCI | National Cancer Institute |
| NED | No Evidence of Disease |
| NHEJ | Non-homologous end-joining |
| NIH | National Institutes of Health |
| nM | Nano Molar |
| NPO | Nothing by mouth |
| NSB1 | DNA-repair protein |
| OATP1B1 | Organic Anion Transport Polypeptide 1b1 |
| OCT2 | Organic Cation Transporter 2 |
| OHRP | Office for Human Research Protections |
| OR | Overall response |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| pADPr | Poly-ADP-ribose |
| PALB 2 | Partner And Localizer of BRCA2 |
| PARP | Poly-ADP-ribose |
| PD | Progressive Disease |
| PDX | Patient-derived xenograft |
| PET | Positron Emission Tomography |
| PFS2 | Progression-free survival 2 |
| PHI | Personal health information |
| PI | Principal investigator |
| PI | Sponsor- Investigator |
| $PO_2$ | Phosphate |
| POD | Progression of disease |
| PR | Partial Response |
| PTEN | phosphatase and tensin homolog |
| QA | Quality Assurance |

| | |
|---|---|
| QD | Once daily |
| Rad51 | a eukaryote gene |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic acid |
| RP2D | Recommended Phase 2 Dose |
| SAE | Severe adverse event |
| sBRCAmut | somatic BRCA mutation |
| SD | Stable Disease |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SGPT | Serum Glutamate Pyruvate Transaminase |
| SOP | Standard Operating Procedure |
| SSB | DNA single-strand breaks |
| TBD | To be decided |
| TEAE | Treatment-Emergent Adverse Event |
| TFST | Time to First Subsequent Treatment |
| Tmax | Time At Maximum Concentration (of drug in serum) |
| TP53 | Tumor Suppressor Gene TP53 (Tumor Protein 53) |
| TUKH | The University of Kansas Hospital |
| UGI | Upper gastrointestinal |
| WBC | White Blood Cells |

## 3 SCHEMATIC OF STUDY DESIGN



# 4 PROTOCOL SUMMARY

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|---|---|
| Title | Niraparib in metastatic pancreatic cancer after previous chemotherapy (NIRA-PANC): a phase 2 trial |
| Protocol Number | IIT-2017-NIRA-PANC |
| Phase | Phase 2 |
| Methodology | Open label single arm |
| Study Duration | Accrual target enrollment of 18 patients over a period of approximately 24 months, followed by 4-6 cycles (28 days per cycle) = approximately 30 months study duration for Primary Objective. |
| Study Center(s) | 1 (The University of Kansas Medical Center (KUMC) with 4 affiliated KU community sites) |
| Objectives | **Primary Objective**: To assess antitumor efficacy of Niraparib using Objective Response Rate in metastatic pancreatic cancers harboring DNA repair defects.<br>**Secondary Objective(s):**<br>1. Estimate Progression Free survival<br>2. Estimate Overall Survival<br>3. Estimate Disease Control Rate<br>4. Estimate the distribution of DOR<br>5. Estimate Adverse Events<br>**Exploratory Objective**: Store tissue and blood for future research. If study meets objectives then plan specific translational projects after trial completion, based on the state of the science at that time. |
| Number of Participants | 18 |
| Diagnosis and Main Inclusion Criteria | Metastatic pancreatic cancer patients with germline or somatic mutation, either already known, or tested after consent to screening tumor tissue analysis in BRCA1/2, PALB2, ATM, NBN, ATR, BRIP1, IDH1/2, RAD51, RAD51B/C/D, RAD54L, CDK12, BARD1, FAM175A, BAP1, CHEK1/2, GEN1, MRE11A, XRCC2, SHFM1, FANCD2, FANCA, FANCC, FANCG, RPA1, ARID1A. |
| Study Product(s), Dose, Route, Regimen | Niraparib 300mg or 200mg by mouth daily for 28 days (1 cycle = 28 days) (200mg dose is for participants whose baseline weight is <77 kg [169.756 lbs] or baseline platelet count is <150,000 µL). |
| Duration of Administration | Until disease progression<br>Estimated per-participant duration of administration until disease progression is 4-6 cycles |
| Reference Therapy | N/A (single arm study) |

| | |
|---|---|
| Interim Monitoring | No special monitoring<br><br>The DSMC of the KUCC is responsible for monitoring participant safety for this trial. |
| Statistical Methodology For Primary Endpoint | Based on the Simon minimax two-stage design, the null hypothesis will be rejected if 3 or more responses are observed in 18 patients, and we will conclude the niraparib is sufficiently active for further study in this patient population. If the study stops at the end of stage 1, or fewer than 3 responses are observed at the end of stage 2, we will fail to reject the null and conclude that niraparib is not sufficiently active in this patient population to pursue further. The response rate with 95% confidence interval will be estimated using the approach described by Koyama (63) |
| Correlative Studies and Sample Banking For Future Research | Samples will be stored. If study objectives are met, specific translational projects will be developed as separate studies, based on the state of the science at that time.<br><br>See section with title *CORRELATIVE STUDIES AND SAMPLE BANKING FOR FUTURE RESEARCH* |
| Stopping Rules | See section with title *STATISTICAL CONSIDERATIONS / STOPPING RULES* |

# 5 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 5.1 Background Information

**Overview of Pancreatic Cancer**

Worldwide, about 277,000 new cases of pancreatic cancers are diagnosed every year, among which approximately 53,670 cases occur in the United States (1-3) Though there has been a modest improvement in detection, which may have possibly contributed to rising incidence, the 5-year overall survival rate has only marginally increased from 5% to 6% over the last 3 decades. (3,4) While currently pancreatic cancer is the third leading cause of cancer-related death in the US among both men and women (approximately 53,000 deaths annually), it is anticipated to become the 2nd leading cause of cancer related deaths in the US in the next decade. (5) More than 50% of pancreatic cancers have distant metastases at the time of initial diagnosis, where median survival ranges from 7-11 months. (6,7) FDA approved first line chemotherapy regimens include gemcitabine plus nab-paclitaxel, or folinic acid (leucovorin), fluorouracil (5-FU) with irinotecan and oxaliplatin (FOLFIRINOX). In patients who have progressive disease following above first line chemotherapy regimens, second line regimens commonly used in clinical practice are 5-FU with oxaliplatin (FOLFOX) or 5-FU with irinotecan (FOLFIRI), and both these regimens resulted in median overall survival (OS) of approximately 6 months, and median progression-free survival (PFS) of 3 months. (8-10) A randomized Phase II clinical trial investigating FOLFIRI versus FOLFOX chemotherapy demonstrated that both regimens were equivalent (PFS 8.3 vs 6 weeks, and OS 16.6 vs 14.9 weeks). (11) Most recently, the liposomal irinotecan agent MM-398 showed median OS of 6.1 months and median PFS of 3.1 months in combination with 5-FU in the randomized international Phase III Napoli -1 study. (12)

**DNA Repair Mechanism and Pancreatic Cancer**

Attempts to improve therapy for patients with pancreatic adenocarcinoma have largely failed to meaningfully improve survival. Therefore, there is a critical need for identification of specific molecular changes that define prognosis and guide therapy decisions. Previous studies indicate that this disease has a complex genomic landscape.(13-15) Numerous DNA repair defects occur through mutations in DNA mismatch repair genes such as MLH1, MSH2 or MSH6 (3-15% incidence), tumor suppressor genes TP53 (tumor protein 53, 50% incidence), and the Fanconi anemia pathway genes BRCA1/2 (breast cancer genes 1,2) and PALB2 (partner and localizer of BRCA2), (7% incidence in sporadic pancreatic cancer, and up to 17% in familial cases), as well as FANCC (Fanconi anemia group C) and FANCG (Fanconi anemia group G) (5-10%).(16-25)

Additional key factors and regulatory pathways in DNA repair including ATM (ataxia-telangiectasia mutated)/Chk2 (checkpoint-like kinase 2), ATR (ataxia-telangiectasia and Rad3-related)/Chk1 (checkpoint kinase 1), Rad51, ERCC1 (excision repair cross-complementation group 1), and PTEN (phosphatase and tensin homolog), can undergo mutation or inactivation in pancreatic adenocarcinoma.(26-32)

Though retrospective studies have shown that among patients with familial pancreatic cancer syndrome, overall, the incidence of BRCA2 mutations is up to 17%, a recent prospective cohort study by Holter et al in 2015 evaluated 306 patients with newly diagnosed pancreatic cancer and found pathogenic germline BRCA2 mutations in 3.6%, and BRCA1 mutations in 1% of patients. (33) Defective DNA damage response pathways in pancreatic cancer represent a targeted opportunity for treatment.

PARP inhibitors exert activity in tumor cells that may not be effectively able to repair initially single-stranded and cumulatively double-stranded DNA breaks and can have a heightened susceptibility in tumor cells over normal tissue. This concept is referred to as synthetic lethality.

**Role of PARP Inhibitors in Pancreatic Cancer**

Poly-(ADP-ribose) polymerases are nuclear enzymes activated by DNA single- (SSB) or double- strand breaks (DSB). These polymerases synthesize poly(ADP-ribose) [pADPr] polymers that result in DNA repair. (34,35) There are seventeen PARP family members classified, but only three (PARP1, PARP2 and PARP3) have recognized roles in DNA repair mechanism. (36)

The best studied PARP enzyme in PARP1 which is essential in DNA repair pathways via multiple mechanisms as follows: 1) base excision repair (BER) which refers to repair of a single damaged base; 2) repair of DSB by recruitment of DNA repair proteins NSB1 and MRE11 to begin homologous recombination (HR) whereby utilizing one copy of a gene as a template for the second copy of the same gene to be repaired; 3) inhibits activation of the non-homologous end-joining recombination (NHEJ) DSB repair pathway which is error-prone; 4) restarts replication forks; 5) alternative end-joining repair; 6) modulates transcription of gene; 7) regulates structure of chromtin; 8) alters activity of microRNA; and 9) affects metabolism of energy. (35,37-48)

Inhibiting PARP enzyme has been exploited as a therapeutic target in breast and ovarian cancers, that harbor HR pathway deficiencies such as BRCA1/2 or PALB2 mutations, in the setting of synthetic lethality by using a PARP inhibitor. (49,50)

Up to the present time PARP inhibitors have exhibited clinical activity as single agents in a subset of pancreatic cancers with BRCA1/2 or PALB2 mutations. Olaparib showed response rate of 22% and median PFS and OS of 4.6 and 9.8 months, respectively in patient population that had progressed on at least 2 lines of prior therapy. Another PARP inhibitor called ABT-888 demonstrated 31% 4 months+ stable disease rate, and a median PFS of about 2 months in refractory pancreatic cancers. (51-53)

Rucaparib was studied in patients with BRCA mutant pancreatic cancer who had been exposed to prior chemotherapy in the locally advanced or metastatic disease setting. 11 male and 8 female patients were enrolled and evaluated. Rucaparib treatment demonstrated an objective response rate of 16%. The disease control rate for all patients was 32% and for those who were exposed to at least one prior line of chemotherapy was up to 50% (54).

ABT-888 showed 31% 4 months+ stable disease rate, and a median PFS of approximately 2 months in refractory disease. (53)

Another phase 2 study showed that PARP inhibitor Olaparib showed 21% overall response rate in BRCA mutant metastatic pancreatic cancer who had received prior chemotherapy. (52)

Therapies for second line metastatic pancreatic cancer are an area of unmet need. Based on above data, it is our assertion that PARP inhibition in metastatic pancreatic cancer given the high incidence of DNA repair pathways abnormalities (up to 25%), this trial expects to observe a clinically meaningful improvement in the primary outcome, Objective Response Rate, with limited toxicity and also to identify the patient population most likely to benefit from this targeted therapeutic approach with retrospective analysis of HRD score.

**Niraparib Clinical Experience (59)**

*Niraparib (formerly MK-4827), or 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1), 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 homologous recombination deoxyribonucleic acid (DNA) repair pathway, as a sensitizing agent in combination with cytotoxic agents and radiotherapy, and in combination with immune-oncology biologics. The niraparib drug product is formulated as a dry-filled capsule (100 mg) for oral administration.*

*In preclinical animal models, maximal in vivo efficacy was achieved in mutant breast cancer-1 (BRCA1mut) ovarian tumor models with once daily oral administration of niraparib at a dose sufficient to suppress 90% of the PARP enzymatic activity in the tumor at 8 hours postdose.*

*Administration of the same dose translated to a >50% inhibition of PARP activity in peripheral blood mononuclear cells (PBMCs) at 8 hours post dose. Clinical development data from the niraparib Phase 1 study demonstrated 50% inhibition of PARP activity in PBMCs at dose levels of ≥80 mg.*

*Nonclinical tests found that tumors containing BRCA mutations or otherwise positive by the myChoice® HRD test regressed in response to niraparib treatment. Moreover, tumor growth inhibition was observed in a subset of HRD negative models, suggesting there is a gradient of response to niraparib that is observed on a population basis by use of different biomarkers.*

*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.*

*In the absorption, metabolism, and excretion (AME) study in cancer patients using 14Cradioactive niraparib, the overall recovery in the excreta following continuous collection up to 21 days was high, suggesting minimal long-term retention of niraparib or its metabolites. Moreover, hepatobiliary clearance and renal excretion are the major routes of elimination in humans.*

*In a dose escalation study in cancer patients, niraparib exhibited linear pharmacokinetics (PK), and dose-proportional exposure. Moreover, the consistent time to maximum concentration (Tmax) and half-life (t½) across the range of doses evaluated (30-400 mg) suggest overall dose independent absorption and clearance. Niraparib was shown to have high oral bioavailability (F ~73%). A high-fat meal exhibited a negligible effect on the extent and rate of absorption of niraparib.*

*The interaction potential of niraparib with major drug-metabolizing enzymes and drug transporters were evaluated in vitro. Based on the overall minimal risk for drug-drug interactions (DDI) delineated in vitro, clinical DDI studies were deemed unnecessary.*

*Niraparib was evaluated in a series of Phase 1 clinical trials in patients with solid tumors. One hundred forty-four 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 recommended Phase 2 dose (RP2D) was determined to be 300 mg QD.*

*The primary efficacy and safety data of niraparib as maintenance treatment in patients with platinum-sensitive recurrent ovarian cancer are derived from a Phase 3 study (NOVA), which included a total of 546 niraparib-treated patients at the time of data cut. Niraparib, as a daily oral treatment, prolonged the effect of platinum-based chemotherapy, improved progression-free survival (PFS), and reduced the risk of recurrence or death in a broad population of patients.*

*Within the germline BRCA mutation (gBRCAmut) cohort, the median PFS was 21.0 months in patients on niraparib versus 5.5 months on placebo (hazard ratio [HR], 0.27; p < 0.0001). PFS was also significantly longer with niraparib in the homologous recombination deficient-positive (HRDpos) group of the non-gBRCAmut (without germline BRCA mutation) cohort (median, 12.9 months versus 3.8 months; HR, 0.38; p < 0.0001) and in the overall non-gBRCAmut cohort (median, 9.3 months versus 3.9 months; HR, 0.45; p < 0.0001).*

*Secondary endpoints, including chemotherapy-free interval (CFI), time to first subsequent treatment (TFST), and progression-free survival 2 (PFS2), confirmed the PFS benefit of niraparib treatment in both cohorts, provided evidence that niraparib does not diminish responsiveness to subsequent therapy, and demonstrates a persistent treatment effect of niraparib.*

*There was no evidence of a detrimental impact of niraparib treatment on overall survival (OS).*

*Dose reductions had no impact on PFS.*

*Patient-reported outcomes data were similar for patients in the niraparib and placebo treatment arms. Data from the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI) and European Quality of Life Scale, 5-Dimensions (EQ-5D-5L) questionnaires showed equivalent outcomes for niraparib versus placebo for both generic and disease-specific outcomes in the gBRCAmut and the overall non-gBRCAmut cohorts.*

*The non-gBRCAmut cohort represents patients with diverse tumor biology. Exploratory analyses were conducted to identify any potential drivers of niraparib treatment effect in these biomarker subgroups (HRDpos/somatic BRCA mutation [sBRCAmut], HRDpos/BRCA wild type [BRCAwt], and HRD negative [HRDneg]). The benefit of niraparib treatment within the HRDpos group as a whole was not due to patients with somatic BRCA mutations. In the HRDpos primary efficacy population, the median PFS for niraparib was similar to that seen in HRDpos/BRCAwt patients. The treatment effect observed in the gBRCAmut cohort was comparable to the results observed in HRDpos/sBRCAmut subgroup. Review of data for patients with BRCA mutations (germline or somatic) combined across both the gBRCAmut and non-gBRCAmut cohorts also showed a significant treatment effect.*

*The overall population of the non-gBRCAmut cohort included patients with tumors that were HRDneg, and exploratory analyses demonstrated that this population experienced a benefit from niraparib treatment. At 18 months, more than twice as many niraparib-treated patients than placebo-treated patients were considered progression-free.*

*Overall, niraparib appears to have a predictable adverse event (AE) profile that is readily managed through routine laboratory testing (i.e., complete blood count [CBC]) and clinical surveillance (i.e., blood pressure monitoring) and adherence to the recommended dose modifications. The most commonly observed non-hematologic treatment-emergent adverse events (TEAEs) (any grades) were nausea, fatigue, constipation, and vomiting; the majority of the non-hematological TEAEs were mild to moderate*

*in severity. The most commonly observed hematologic TEAEs (any grades) were anemia, thrombocytopenia, and neutropenia. The incidence of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) in patients who received niraparib was similar to that in patients who received placebo. Although Grade ¾ hematologic laboratory events were common at the initiation of treatment, no severe clinical sequelae were observed and relatively few patients discontinued due to these AEs. Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these events beyond Cycle 3.*

Based on the above trial, Niraparib is now FDA approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

The DNA-repair pathway should be further studied and genomic characterization beyond BRCA1/2/PALB2 mutations need to be identified in order to consider a personalized therapeutic approach in a larger patient population. For example, Preclinical studies have shown that Mismatch Repair deficiency cell lines are sensitive to PARP inhibition.(55)

There are other DNA repair genes reported in the literature that are associated with cancer-predisposition syndromes.(65)

Breast cancer cells that are deficient RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHK1, CHK2, FANCD2, FANCA, or FANCC have been demonstrated to be sensitive to PARP inhibition. (64)

**Rationale for BROCA-HR and HRD Score as predictive biomarkers for banking and future correlative studies**

Various mechanisms result in HR deficiency hence it is not possible for a single test to detect all patients with the HRD (or BRCA ness) phenotype. In addition to gene mutations that lead to HRD, other mechanisms such as gene rearrangements, DNA methylation and mRNA expression can also lead to HRD. Therefore, assays have been developed and many are being developed to evaluate homologous recombination (HR) DNA repair in order to detect subsets of Pancreatic cancer patients with HRD. These assays can serve as biomarkers that could allow to select a subset of patients for future clinical trials to investigate DNA- damaging agents like PARP inhibitor.

One such assay is the Myriad Genetics HRD test that has been assessed in breast and ovarian cancer clinical trials using PARP inhibitors and/or other DNA damaging agents, and have demonstrated correlations with clinical outcomes. It was found that HRD positive breast and ovarian tumors with an HRD score of ≥ 42 or a deleterious mutation in BRCA1/2 gene correlated with clinical outcomes. Although the primary clinical application of the HRD score will be to enrich for responders to HR targeted therapies, this will not the criteria for selecting the threshold. Despite the fact that the essential clinical use of the HRD score will be to enrich for responders to HR targeted therapies, this won't be the criteria for choosing a threshold score. A threshold HRD score is yet to be defined for pancreatic cancers. Hence HRD score will not be utilized to select patients for the proposed NIRA-PANC clinical trial.
NOTE: Myriad Genetics HRD analysis, if performed, will be undertaken under a separate study on stored tissue after this trial is completed.

## 5.2 Study Agent(s) / Treatment(s)

**Background of Niraparib (59)**

*Niraparib is an orally available, potent, highly selective PARP-1 and -2 inhibitor. Niraparib co-crystallized with the human PARP-1 catalytic domain and was shown to inhibit PARP-1 and PARP-2 activity in vitro with an inhibitory concentration (IC50) of 3.8 and 2.1 nM, respectively. In cultured cells, niraparib inhibited PARP-dependent PARylation stimulated by DNA damage with an IC50 of 4 nM and an IC90 of 40 nM.*

*Niraparib demonstrated 25- to 200-fold increased selectivity against cancer cell lines that were engineered to be homologous recombination deficient via BRCA1 or BRCA2 silencing, or that carried BRCA1 or BRCA2 mutations, as compared to their wild type counterparts. Treatment of xenograft-bearing mice at clinically relevant doses resulted in tumor regression in BRCA and ATM tumor models. At these dose levels, 90% PARP inhibition was observed in tumors for up to 24 hours after a single dose and was greater and more durable than PARP inhibition in the corresponding PBMCs, where inhibition levels were 50% or less by 24 hours postdose.*

*Niraparib has also been evaluated in more than 30 ovarian cancer patient-derived xenograft (PDX) and tumor cell line xenograft models. Tumor regression has been observed in BRCA1 and BRCA2 mutant xenografts and in HRDpos wildtype BRCA models. Additionally, tumor growth inhibition was observed in some models that were HRDneg.*

*Currently, few PARP inhibitors are in clinical development. PARP inhibitors vary in their mechanisms of action, PK properties, and safety profiles.*

**Absorption and Pharmacokinetics**

*In rats and dogs, niraparib was rapidly absorbed (Tmax ~ 2 and 0.5 hours, respectively), orally bioavailable (F ~ 27 and 57%, respectively), had extensive tissue distribution (Vdss ~6.9 and 12.3 L/kg, respectively), and had a slow to moderate rate of metabolism, resulting in moderate to long terminal elimination half-lives (t1/2 ~3.4 and 5.7 hrs, respectively) (Study PK001). Niraparib is readily distributed to the brain of rats and the cerebrospinal fluid (CSF) of monkeys. For instance, in rats the brain-to-plasma Cmax ratios were 0.77 and 0.64 following oral (PO) doses of 10 and 30 mg/kg, respectively. The CSF-to-plasma Cmax ratio was approximately 0.31, with the CSF-to-plasma AUC0-$\infty$ ratio of 0.19 after a PO dose of 10 mg/kg in monkeys (Study KB-0039- DA-RI and Study PK004).*

***Distribution***

*Niraparib was moderately bound to plasma proteins (Fu ~16.0-28.4%), and RBCs, with blood-to-plasma concentration ratios of 1.1-1.7 across species (Study PK002 and Study PK004). More importantly, the compound is highly cell membrane-permeable (Study PK002, Study PK004, and Study 15TESAP3). The high cell permeability, high volume of distribution, and moderate brain penetration seen for niraparib appear to be consistent and interconnected. The compound elicited appreciable intestinal absorption and feasibly crossed blood-brain barrier, with the counter efflux from P-glycoprotein (P-gp) being evidently limited.*

***Metabolism***

*The metabolic profiles detected in the experimental species in vivo and observed in the liver enzyme systems from those experimental species and human in vitro were consistent (Study PK002 and Study PK003). For instance, the major metabolic pathways leading to the formation of the principal*

*circulating metabolites, the carboxylic acid (M1) and the subsequent glucuronide conjugate (M10), appeared to be species-independent, and thus common to rats, dogs, and humans. In the liver microsomal preparations and the hepatocyte suspensions from humans, rats, and dogs, niraparib turnover was generally slow, in accordance with the modest rate of biotransformation in vivo, whereas the formation of amide-hydrolyzed metabolite (M1) and oxidative metabolites (M2, M3, M8, and M10) were detected after a 2-hour incubation.*

*The human metabolites of niraparib were all observed in rats, and most were observed in dogs in vitro. Although multiple drug-metabolizing enzymes in a few enzyme families are responsible for the metabolism of niraparib across the species studied, carboxylesterases (CEs) played a key role in hydrolyzing the amide of niraparib in human liver microsomal preparations (Study PK002). Hydrolysis was, however, not observed in fresh blood obtained from rats, dogs, and humans, consistent with the high stability of the compound in plasma. The minor oxidative pathways were primarily mediated by CYP1A2 and CYP3A4/5 with a possibly minor contribution from CYP2D6. However, the CYP-mediated pathways, if any, appeared to be minimal in the treatment setting; the oxidative metabolite in circulation was not detected in cancer patients following the administration of the recommended therapeutic dose (i.e., 300 mg) (PR-30-5015-C). Therefore, the CE-mediated hepatic clearance, with a negligible contribution from the drug-metabolizing cytochrome P450 (CYP) enzymes, warrants a minimal risk of DDI for niraparib when being administered concurrently with CYP inhibitory and/or inductive* agents.

***Excretion***
*The major routes of elimination of niraparib were determined to be both renal and fecal. Niraparib was primarily eliminated unchanged via fecal and renal routes in rats, while being mainly eliminated as M1 via renal excretion in dogs. The overall recoveries in rats and dogs were high and virtually identical, suggestive of minimal long term body retention (approximately 80% for 5-day collections for both species) (Study PK003). Elimination in the experimental species, with respect to the route and recovery, was consistent with that detected in humans*

***Drug Interaction Potential and CYP-mediated Drug Interactions***
*Niraparib was evaluated in vitro for the potential risk of DDIs, and delineated to be neither a reversible inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5, nor a time-dependent inhibitor (TDI) of CYP3A4/5 (Study PK002). At a concentration of 20 µM (approximately five times higher than mean Cmax detected in the clinic following the administration of the recommended therapeutic dose), niraparib did not induce CYP3A4 at the level of either messenger ribonucleic acid (mRNA) expression or enzyme activity in cultures of human hepatocytes. A potential elevation in CYP1A2 activity in vitro was detected. Such an effect was characterized to be weak (e.g., with a maximum induction of approximately 26% relative to omeprazole, a prototypic CYP1A2 inducer) and concentration- dependent, observed only following the exposure to the high concentration of compound (i.e., ≥5 µM), which is unlikely to be clinically relevant. Moreover, M1, the major primary circulating metabolite in humans, was also evaluated for CYP inhibition and induction potential. M1 did not show major inhibition of any major hepatic drug-metabolizing CYPs, and was not an inducer of CYP1A2 or CYP3A4 (Study KB-0081-DV-BADB).*

***Transporter-mediated Drug Interactions***
*Niraparib was determined to be a substrate of P-gp and a substrate and an inhibitor of breast cancer resistance protein (BCRP) (Study PK002 and Study 15TESAP1R2). However, neither niraparib nor the major metabolite M1 was found to interact with any of the major hepatic and renal uptake*

*transporters, namely organic anion transport polypeptide 1B1(OATP1B1), 1B3 (OATP1B3), organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2). Furthermore, neither compound elicited any potential to interact with bile salt export pump (BSEP), an efflux transporter known to be associated with hepatotoxicity (Study 15TESAP1R2).*

***Summary of Nonclinical Pharmacokinetics***

*The absorption, distribution, metabolism, and elimination (ADME) of niraparib in the nonclinical species, including the toxicological models, has been delineated. The key findings are highlighted as follows:*

- *Rapid and high absorption*
- *Extensive distribution to the tissues*
- *Metabolic pathways and the resulting profiles are consistent across species, including rat, dog, and human*
- *Amide hydrolysis, catalyzed by CEs, is the main hepatic clearance mechanism*
- *Cytochromes P450 play a minimal role in niraparib metabolism. UDP-glucuronosyltransferases (UGTs) are responsible for the Phase 2 pathway (glucuronidation)*
- *The major primary metabolite is the carboxylic acid (M1), which is subsequently converted to the glucuronide (M10)*
- *Elimination via both renal and fecal routes in the nonclinical species, as well as in humans*
- *Neither niraparib nor M1 is an inhibitor of any hepatic drug-metabolizing CYP enzymes, and neither compound is an inducer of CYP3A4*
- *Niraparib, but not M1, is a weak inducer of CYP1A2 in vitro at high concentration (≥ 5 µM); this finding is likely clinically irrelevant*
- *Niraparib, but not M1, is a substrate for P-gp and a substrate and an inhibitor of BCRP*
- *Neither niraparib nor M1 is an inhibitor of BSEP proteins*
- *Neither niraparib nor M1 is a substrate or an inhibitor of any major renal and hepatic uptake transporters, including OATP1B1, OATP1B3, OAT1, OAT3, and OCT2.*

*Collectively, the nonclinical in vivo and in vitro studies of metabolism and PK exhibited a preferable disposition profile of niraparib with a minimal DDI potential for oral once daily dosing, consistent with the development of the compound as an agent for use in patients with cancer, including those with ovarian, breast, and prostate cancers.*

***EFFECTS IN HUMANS***

***Overview: Ongoing and Completed Studies (Design and Status)***

*Niraparib is currently under investigation for several non-hematologic malignancies, including ovarian, breast, and prostate cancers.*

*Six Phase 1 clinical studies (PN001, PN005, PN008, PN011, and PN014) were conducted in a total of 144 patients. The initial study with niraparib, PN001, was a Phase 1 multiple ascending dose (MAD) study conducted in 2008 by Merck Sharpe and Dohme (MSD). In this study, 300 mg niraparib administered orally QD was determined to be the maximum tolerated dose (MTD) of niraparib monotherapy, in consideration of clinical and PK/pharmacodynamics (PDy) data. In this early phase study, clinical activity of niraparib was observed among patients with various advanced/refractory tumor types, particularly among ovarian and prostate cancer patients, including those with and without BRCA mutations. MSD also conducted 3 other Phase 1 MAD studies with niraparib administered in combination with other chemotherapies in patients with advanced solid tumors that provide additional safety data (Study PN008, Study PN011 and Study PN014).*

*A decision was made by MSD to suspend new enrollment in Studies PN001, PN005, PN008, PN011, and PN014 for non-clinical reasons. Study PN005 was designed to evaluate the recommended clinical dose, the safety, tolerability, PK, and efficacy of niraparib in Japanese patients with solid tumors. Only 3 patients were enrolled in the study prior to termination. As minimal data are available, it is not discussed here.*

*Table 12 presents a summary of TESARO-sponsored clinical trials of niraparib in patients with advanced cancer. Currently, there are 8 ongoing TESARO-sponsored studies (including 2 substudies, one of which [PR-30-5011-C2, FE substudy] is complete) of niraparib alone or in combination with pembrolizumab in patients with advanced ovarian or advanced breast cancer. Overall, the safety and tolerability of niraparib has been evaluated in over 800 patients who received at least 1 dose of niraparib in TESARO-sponsored studies.*

*TESARO, in partnership with Janssen Research & Development, LLC., is investigating niraparib in combination with apalutamide in a Phase 1 trial in patients with advanced prostate cancer associated with DNR-repair gene anomalies (Study 64091742PCR1001), and in a Phase 2 study of niraparib in men with advanced prostate cancer previously treated with at least 1 taxane-based therapy and at least one line of androgen receptor (AR) directed therapy (Study 64091742PCR2001).*

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

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

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

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

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

Based on the above trial, Niraparib is now FDA approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

**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 (<180 109/L) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76%) or Grade ≥ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg [169.756 lbs] 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 [169.756 lbs] 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 [169.756 lbs] 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) in participants whose baseline weight is <77 kg [169.756 lbs] or baseline platelet count is <150,000 µL.

***Overview of Clinical Studies of Niraparib***



**Table 12: Overview of Clinical Studies of Niraparib**

| Study ID | No. of Centers (Location) | Study Dates (Status) | Total Enrollment (Planned/ Actual) | Design / Control | Route and Regimen | Indication | No. of Patients by Treatment (Entered/ Treated) | Median Treatment Duration (cycles, days, or months) | Sex (M/F) Age (Range) Race |
|---|---|---|---|---|---|---|---|---|---|
| **Phase 1** | | | | | | | | | |
| PN001 | 3<br>(US, UK) | 15 Sep 2008 – 14 Sep 2011<br>Completed | 50 to 342/104 | Open-label MAD | Niraparib: 30, 40, 60, 80 , 110, 150, 210, 290, 300, 400 mg PO QD | Advanced ST or hematologic malignancies | Total: 104/104 | 58.5 days | 31/73<br>35-75<br>W: 99<br>B: 2<br>A: 1<br>Unk: 2 |
| PN008 | 2<br>(US, UK) | 13 Jul 2010 - 04 Jul 2011<br>Terminated | 105/12 | Open-label MAD | Niraparib: 40, 60, 80, 110 mg PO QD for 4 days each 21-day cycle starting 2 days before carboplatin administered on Day 3 | Advanced ST | Total: 12/12<br>3/dose level (40, 60, 80, 110 mg) | 6 cycles | 2/10<br>30-74<br>W: 11<br>B: 1 |
| PN011 | 3 (US, Israel) | 17 Nov 2010 - 14 Sep 2011<br>Terminated | 90/6 | Open-label MAD | Niraparib: 30 or 40 mg QD PO on Days 1-16 of 28-d cycles<br>Pegylated liposomal doxorubicin: 40 mg/m$^2$ IV on Day 3 of every 28-day cycle | Advanced ST | Total: 6/6 3/dose level (30 and 40 mg) | 3.5 cycles<br>(Days 1-16 of 28-d cycles) | 3/3<br>44-67<br>W: 6 |

**Table 12: Overview of Clinical Studies of Niraparib (Continued)**

| Study ID | No. of Centers (Location) | Study Dates (Status) | Total Enrollment (Planned/ Actual) | Design / Control | Route and Regimen | Indication | No. of Patients by Treatment (Entered/ Treated) | Median Treatment Duration (cycles, days, or months) | Sex (M/F) Age (Range) Race |
|---|---|---|---|---|---|---|---|---|---|
| PN014 | 3 (US) | 28 Feb 2011 - 14 May 2012 Terminated | 64/19 | Open-label MAD | Niraparib: 30, 40, 70 mg QD PO on Days 1-8 of 28- day cycles<br>Temozolomide: 150 mg/m$^2$ IV on Days 4-8 of every 28-day cycle | Advanced ST | Total: 19/19 6 (30 mg)<br>10 (40 mg)<br>3 (70 mg) | 30 mg: 41.5 days<br>40 mg: 37.5 days<br>70 mg: 46.0 days | 5/14<br>25-78<br>W: 17<br>B: 2 |
| PR-30-5015-C AME | 1 (Nether-lands) | 29 Jan 2015 - Ongoing, closed to enrollment (Data cut: 15 Feb 2016) | Part 1: 6/6<br>Part 2: 6/6<br>Extension: 12/11 | Open-label<br>2 part:<br>AME, absolute BA with treatment extension | Niraparib:<br>Part 1: single dose 300 mg PO + IV [$^{14}$C] 100 µg<br>Part 2: [$^{14}$C] single dose 300 mg PO<br>Extension: 300 mg QD PO | Advanced ST | Total Part 1 and Part 2: 12/12<br>Extension: 11/11 (3 ongoing) | Parts 1 and 2: Single dose<br>Extension:67 days | 0/12<br>33-71<br>W: 12 |
| 64091742PC R1001 (Janssen) | 6 (US, Canada) | Ongoing enrolling. (Data cut: 06 Oct 2016) | 0 | Open-label<br>2 phases: dose escalation and evaluate RP2D | Niraparib: 100, 200, or 300 mg QD PO of 28- day cycles<br>Apalutamide: 240 mg QD PO of 28- day cycles | Men with mCRPC previously treated with at least one line of taxane-based chemotherapy and at least one line of AR-targeted therapy | 0 | Not available. | 0/0 |

**Table 12: Overview of Clinical Studies of Niraparib (Continued)**

| Study ID | No. of Centers (Location) | Study Dates (Status) | Total Enrollment (Planned/ Actual) | Design / Control | Route and Regimen | Indication | No. of Patients by Treatment (Entered/ Treated) | Median Treatment Duration (cycles, days, or months) | Sex (M/F) Age (Range) Race |
|---|---|---|---|---|---|---|---|---|---|
| **Phase 1/2** | | | | | | | | | |
| 3000-PN162-01-001 (TOPACIO) | Phase 1: ~6 centers (US)<br>Phase 2: ~40 (global) | Ongoing, enrolling. Data cut: 6 Oct 2016 | Phase 1: Approximately 18 patients (up to 36 patients may be included)<br>Phase 2: Approximately 96 patients | Open-label<br>2 phase: dose escalation and evaluate RP2D | Niraparib: 100, 200, or 300 mg QD PO of 28- day cycles<br>Pembrolizumab: 200 mg IV on Day 1of each 28-day cycle | Triple negative breast or recurrent ovarian cancer | Ongoing | Not available | 0/13<br>43-72<br>W: 12<br>Other: 1 |
| **Phase 2** | | | | | | | | | |
| PR-30- 5020-C QUADRA | 39 (US) | 27 Mar 2015 - Ongoing, enrolling (Data cut: 20 May 2016) | 400/311 | Open-label Treatment | Niraparib: 300 mg QD PO in continuous 28-day cycles | Advanced, relapsed (≥3 prior lines of therapy), high grade serous epithelial OC | 311/291<br>(139 ongoing on study) | 1.9 months | 0/291<br>29-90<br>W: 243<br>B: 18<br>A: 9<br>AI: 1 |
| 64091742PCR2001 (Janssen) | ~100 (US, Canada, Belgium, Germany, Sweden, UK, France, Italy, Spain, Netherlands, Denmark, Russia, Australia, South Korea) | Ongoing, enrolling. (Data cut: 06 Oct 2016) | 1/100 | Open-label Treatment | Niraparib: 300 mg QD PO in continuous 28 day cycles | Men with mCRPC and DNA-repair anomalies who have had at least 1 line of taxane-based chemotherapy and at least 1 line of AR-targeted therapy | 1/1 | 5 days | 1/0<br>55 (55-55)<br>Unk: 1 |

**Table 12: Overview of Clinical Studies of Niraparib (Continued)**

| Study ID | No. of Centers (Location) | Study Dates (Status) | Total Enrollment (Planned/ Actual) | Design / Control | Route and Regimen | Indication | No. of Patients by Treatment (Entered/ Treated) | Median Treatment Duration (cycles, days, or months) | Sex (M/F) Age (Range) Race |
|---|---|---|---|---|---|---|---|---|---|
| **Phase 3** | | | | | | | | | |
| PR-30-5011-C NOVA | 107 (North America, Europe, Israel) | 26 Aug 2013 - Ongoing, closed to enrollment (Data cut: 30 May 2016; Data lock: 20 June 2016) | 490/553 | Randomized, double-blind, placebo-controlled Maintenance | Niraparib: 300 mg QD PO in continuous 28-day cycles | Women with platinum-sensitive recurrent OC with CR or PR to their most recent platinum-based therapy | 553/546 (382 ongoing) Niraparib: 372/367 (266 ongoing on study) Placebo: 181/179 (116 ongoing on study) | Niraparib: 250 days Placebo: 163 days | 0/546 33-84 W: 480 B: 7 A: 19 AI: 1 Unk: 46 |
| PR-30- 5011-C1- QTC QTc substudy | 4 (US) | 28 May 2015 - Ongoing, closed to enrollment (Data cut: 30 May 2016) | 20/26 | Open-label ECG evaluation with treatment extension | Niraparib: 300 mg QD PO | Women previously treated with recurrent OC | 26/26 (10 ongoing on study) | 151.5 days | 0/26 46-76 W: 21 B: 3 A: 1 AI: 1 |

**Table 12: Overview of Clinical Studies of Niraparib (Continued)**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PR-30- 5011-C2- FE<br>FE substudy | 6 (US) | 05 Aug 2013 – 20 Oct 2015<br>Complete | 12/17 | Open-label Fasted vs fed crossover with treatment extension | Niraparib: 300 mg single dose PO For extension: 300 mg QD PO | Women with previously treated recurrent OC with no standard therapy options | 17/17 | 42 days | 0/17<br>47-69<br>W: 15<br>B: 1<br>NH: 1 |
| PR-30- 5010-C BRAVO | 109<br>(North America, Europe, Israel) | 08 Apr 2014 - Ongoing, enrolling (Data cut off: 15 Mar 2016) | 306/141 | Randomized, open-label versus Physician's choice | Niraparib: 300 mg QD PO Eribulin, vinorelbine, gemcitabine, or capecitabine | Adults with previously-treated advanced, metastatic, HER2-negative gBRCAmut breast cancer | Total: 141[a] | NA[a] | NA[a] |
| PR-30-5017-C (PRIMA) | ~180 (global) | Ongoing, enrolling; no data available | 350 (planned) | Double-blind, randomized, placebo-controlled (2:1 niraparib: placebo) | Niraparib: 300 mg QD PO in continuous 28 day cycles | Stage III or IV ovarian cancer | Not available | Not available | Not available |

Abbreviations: A = Asian; AI = American Indian or Alaska Native; AME = absorption, metabolism, and excretion; B = Black; BA = bioavailability; CR = complete response; d = day; FE = food effect; gBRCAmut = germline BRCA mutation; HER2 = human epidermal growth factor receptor 2; IV = intravenous; mCRPC = metastatic castration-resistant prostate cancer; MAD = multiple-ascending dose; NA = not applicable; NH = Native Hawaiian or other Pacific Islander; OC = ovarian cancer; PO = oral; PR = partial response; QD = once daily; QTc = QT interval corrected for heart rate; ST = solid tumor; UK = United Kingdom; Unk = unknown; US = United States; W = White

[a] BRAVO study is still open to enrollment and has not yet completed its primary efficacy analysis (final progression-free survival analysis and overall survival analysis). As such, and in agreement with the Sponsor partner in the study (Breast International Group and EORTC), the Sponsor is blinded to aggregate data by study arm to avoid perception of impact to the conduct of the study.

## 5.3 Other Agent(s) / Treatment(s)

Not applicable – single - agent study

## 5.4 Rationale For Main Study

**Study objective**: The primary objective of the trial is to assess antitumor efficacy of Niraparib using Objective Response Rate (ORR) in metastatic pancreatic cancers harboring DNA repair defects.

**Study Design Justification**
Beyond first-line therapy, options for metastatic pancreatic cancer become less clear, as patients often demonstrate rapid clinical deterioration and are no longer suitable candidates for additional treatment beyond best supportive care. One co-operative group trial reported that only 45% of patients with metastatic pancreatic cancer went on to receive additional therapy following progression on front-line study treatment (Schrag et al). A number of small prospective single-arm studies have evaluated both cytotoxic and/or targeted agents in the setting of gemcitabine-refractory disease, generally demonstrating low response rates and progression-free survival of a few months at best. Hence designing a single-arm phase 2 study to assess response rates of study drug(s) in second line setting for metastatic pancreatic cancer is justifiable.

**Study Design**
Single arm phase 2

**Schedule of Procedures:**
Screening
**Biomarker testing – required for participants**

Before signing consent for the main study, potential participants will be asked to consent to screening biomarker testing (unless biomarker information from previous testing is already known) of their tumor tissue in order to determine eligibility for the main study.

For the biomarker testing, potential participants should have availability of either formalin‐fixed, paraffin‐embedded archival tumor from the primary or recurrent cancer for integral biomarker analysis.

Archival tumor tissue will be processed by the KUCC correlative labs as described below.

If archival tumor tissue is not available, or if there is not enough tissue in the archival specimens for testing, potential participants will be asked to allow a new biopsy to obtain integral biomarker analysis.

For archival tumor tissue (this could be either from the biopsy tissue OR tissue gained in previous surgery), 10 unstained Superfrost Plus slides cut at a 10 micron thickness from the most representative and tumor cell enriched block along with the corresponding pathology report should be submitted. These slides will be used for H&E staining and DNA extraction for mutational analysis using a custom next-generation sequencing (NGS) panel targeting the genes listed here: BRCA1/2, PALB2, ATM, NBN, ATR, BRIP1, IDH1/2, RAD51, RAD51B/C/D, RAD54L, CDK12, BARD1, FAM175A, BAP1, CHEK1/2, GEN1, MRE11A, XRCC2, SHFM1, FANCD2, FANCA, FANCC, FANCG, RPA1, ARID1A. The biomarker analyses for NGS will be performed

through the Clinical Molecular Oncology Lab, a CAP-accredited, CLIA certified facility at KUMC (Director: Andrew K. Godwin). The H&E staining will be performed through the CLIA certified histopathology laboratory that is part of the BRCF at KUMC (Director Dr. Andrew Godwin).

Biomarker analysis will be done by KU Clinical Molecular Oncology Laboratory (CMOL). The biomarker test itself, is not a U.S. FDA-approved test. This test was developed and its performance characteristics determined by the CAP-accredited, CLIA certified Clinical Molecular Oncology Laboratory which is qualified to perform high complexity clinical laboratory testing. The test is used for clinical purposes at the University of Kansas Cancer Center as part of patients' standard of care for genetic testing. It has been given an NSR (Non-Significant Risk) determination by the Institutional Review Board overseeing this trial, the KUMC Human Subjects Committee. Patients will not be given specific results from this testing.

**NOTIFICATION OF BIOMARKER TEST RESULTS**
If biomarker testing reveals a mutation that meets study eligibility criteria, then participants will be notified of the specific mutation.

The research team can tell the patients that the mutation found on the screening biomarker testing may have resulted in their development of pancreatic cancer, may impact their risk of developing other cancers, and also impact cancer risk in their family members. Further discussions regarding the role of germline testing and referral to genetic counseling will be deferred to the treating physician and patient. If the patient chooses to undergo germline testing to confirm the mutation then germline testing would be performed free of cost by the study and a report will be provided to the treating physician for further action. If the treating physician and patient choose to pursue genetic counseling and testing family members, if required, it would be considered a standard of care procedure.

Participants will be asked to consent to OPTIONAL storage of tissue from the screening biopsy for banking and future unspecified research.

NOTE: Participants whose biomarkers are already known at screening will also be offered an optional biopsy for tissue storage and future research.

### 5.5 Study Risk / Benefit Ratio

The potential benefit of this study is judged to outweigh risk; therefore, the risk/benefit ratio is in favor of benefit.

## 6 STUDY OBJECTIVES

### 6.1 Primary Objective

The primary objective of the trial is to assess antitumor efficacy of Niraparib using Objective Response Rate in metastatic pancreatic cancers harboring DNA repair defects.

#### 6.1.1 Primary Objective MEASURE

RECIST version 1.1

## 6.2 Secondary Objective(s)

1. Estimate Progression Free survival
2. Estimate Overall Survival
3. Estimate Disease Control Rate
4. Estimate the distribution of DOR
5. Estimate Adverse Events

### 6.2.1 Secondary Objective MEASURES

All measures are: CT/MRI scans, RECIST v 1.1 and CTCAE v 5.0
The imaging modality used at screening must be used for that participant throughout this study. In the event the participant is intolerant to the contrast agent, an alternative imaging modality may be used.

## 6.3 Exploratory Objective(s)

1. Tissue and Blood including DNA will be collected at baseline and at end of treatment (EOT) for storage at KU Biospecimen Repository for unspecified future research. Specific translational projects will be determined after trial completion and if trial proves efficacy of the study drug, based on the state of the science at that time. One example of a possible translational project is evaluation of the impact of Homologous Recombination Deficiency (HRD) score on clinical outcomes. These correlative studies may seek to elucidate a new mechanism of action of Niraparib.

### 6.3.1 Exploratory Objective MEASURE

Not applicable / none
Measures will be undertaken as a separate study in the future.

# 7 STUDY DESIGN AND ENDPOINTS

## 7.1 Description Of The Study Design

Single arm phase 2 trial
Accrual target enrollment of 18 patients over a period of approximately 24 months, followed by 4-6 cycles (28 days per cycle) = approximately 30 months study duration for Primary Objective.
Per funder requirement, patients are followed for MDS/AML and secondary cancers for 4.5 years following last study drug dose. Hence, estimated total study duration is approximately 7 years.

### 7.1.1 Primary **Endpoint**

Objective Response Rate (ORR) based on RECIST criteria 1.1 - calculated at end of 8 weeks of study treatment.

### 7.1.2 Secondary **Endpoint(s)**

All secondary endpoints occur at the date of last follow up:

1. Progression free survival measured as time from initiating study treatment to progression or death.
2. Survival measured as time from initiating study treatment to death from any cause or censored at the date of last follow up.
3. Disease Control is the occurrence of complete response, partial response or stable disease at 8 weeks as defined by RECIST criteria 1.1.
4. Duration of response measured as the time interval from response (CR+PR) until progression or censored at the date of last follow up.
5. Adverse events as defined per CTCAE version 5.0.

Secondary Endpoint Timeframe

Start: End of 8 weeks of treatment until completion of follow-up

### 7.1.3 Exploratory **Endpoint(s)**

Not applicable – samples will be stored for future research and exploratory research will be undertaken as a separate study.

## 8 STUDY ENROLLMENT AND WITHDRAWAL

### 8.1 Participant Inclusion Criteria

Participants must meet **all** of the inclusion criteria listed below to participate in this study.

1. Screening tumor tissue analysis positive with germline or somatic mutation in BRCA1/2, PALB2, ATM, NBN, ATR, BRIP1, IDH1/2, RAD51, RAD51B/C/D, RAD54L, CDK12, BARD1, FAM175A, BAP1, CHEK1/2, GEN1, MRE11A, XRCC2, SHFM1, FANCD2, FANCA, FANCC, FANCG, RPA1, ARID1A.
2. Ability of participant OR Legally Authorized Representative (LAR) to understand this study, and participant or LAR willingness to sign a written informed consent.
3. Age ≥ 18 years.
4. Able to swallow oral study drug
5. ECOG Performance Status = 0 -- 1 (*Appendix A.*).
6. Histologically or cytologically confirmed adenocarcinoma of the exocrine pancreas
7. Measurable disease according to RECIST 1.1
8. Patients with history of other, non-pancreatic cancers with no evidence of active disease are eligible.

9. Participants who have had ANY prior chemotherapy as **first line and/or second line** therapy for metastatic disease are eligible to seek enrollment. Prior adjuvant/neoadjuvant therapy will be counted as first line if progression within 6 months. However, Patients who refuse chemotherapy or do not tolerate chemotherapy are also eligible.
10. Patients must have adequate organ function, defined as follows
    a. Absolute neutrophil count ≥ 1,500/µL
    b. Platelets ≥ 100,000/µL
    c. Hemoglobin ≥ 9 g/dL
    d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using the Cockcroft-Gault equation

e. Total bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤ 1 x ULN
f. Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN

11. Women must have a negative serum pregnancy test within 72 hours to taking study treatment.
12. Women of child-bearing potential and men with partners of child-bearing potential must agree to practice sexual abstinence, or to use the forms of contraception listed below, prior to study entry, for the duration of study participation, and for ***180* days** following completion of therapy. If a woman becomes pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy;
  **or**
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months) and is < 45 years of age.

Men of child-bearing potential must not donate sperm while on this study and for ***180 days*** after their last study treatment.

Acceptable birth control methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence, if this is the preferred and usual lifestyle of the participant

## 8.2 Participant Exclusion Criteria

Participants meeting **any** of the exclusion criteria listed below at screening will be excluded from study participation.

1. Patients simultaneously enrolled in any therapeutic clinical trial
2. Patients have had investigational therapy administered ≤ 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study
3. Current or anticipated use of other investigational agents while participating in this study.

4. Patient has had prior treatment with a known PARP inhibitor
5. Psychiatric illness/social situations that would limit compliance with study requirements.
6. Pregnant, breast feeding or expecting to conceive children while receiving study treatment and for 180 days after the last dose of study treatment. There is a potential for congenital abnormalities and for this regimen to harm breast feeding infants (if applicable)
7. Patients must not have a known hypersensitivity to the components of niraparib or the excipients
8. Patients must not have had major surgery ≤ 3 weeks of starting the study and patient must have recovered from any effects of any major surgery
9. Patients must not have had radiotherapy encompassing > 20% of the bone marrow within 2 weeks or any radiation therapy within 1 week prior to Day 1 of protocol therapy
10. Patients must not be immunocompromised. Patients with splenectomy are allowed
11. Patients must not have received a transfusion (platelets or red blood cells) ≤ 4 weeks of the first dose of study treatment
12. Patients must not have current evidence of any condition, therapy, or laboratory abnormality (including active or uncontrolled myelosuppression [i.e., anemia, leukopenia, neutropenia, thrombocytopenia]) that might confound the results of the study or interfere with the patient's participation for the full duration of the study treatment or that makes it not in the best interest of the patient to participate
13. Patients must not have 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.
14. Patients must not have received colony stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte macrophage colony stimulating factor, or recombinant erythropoietin) within 4 weeks prior initiating protocol therapy.
15. Patients must not have known, symptomatic brain or leptomeningeal metastases
16. Patients must not be considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent
17. Patient must not have any known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)

## 8.3 Participant Withdrawal Or Termination

### 8.3.1 Reasons For Withdrawal Or Termination

Participants can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator. The reason(s) for discontinuation will be documented and may include:

- Participant voluntarily withdraws from treatment (follow-up permitted);
- Participant withdraws consent (termination of treatment and follow-up);
- Participant is unable to comply with protocol requirements;
- Participant demonstrates disease progression;
- Participant experiences toxicity that makes continuation in the protocol unsafe;
- Inter-current illness that prevents further administration of treatment

- Treating physician judges continuation on the study would not be in the participant's best interest;
- Participant becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- Lost to follow-up – **NOTE:** Per funder, TESARO, for patients 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 patient before the patient is deemed lost to follow-up.

### 8.3.2 Participant Replacement

Participants will not be replaced.

# 9 MEASUREMENT OF EFFECT

## 9.1 Solid Tumor

### 9.1.1 Antitumor Effect

Tumor assessments will be performed throughout the study period and analyzed using Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.1 [57]) criteria. Computed tomography (CT) (or MRI if CT contra-indicated) scans will be performed every 8 weeks (WINDOW = +/- 7 DAYS).

Toxicity assessments and management will be performed based on CTCAE ver. 5.0 guidelines as a standard of care.

This study will use RECIST Version 1.1 (57) for evaluation of response and progression.

**Definitions**
Evaluable for toxicity. All participants will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for objective 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 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.)
**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 with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

**NOTE 1**: ***Lymph*** nodes may be identified as target lesions if they have a short axis ≥15mm by CT. Only the short axis of these nodes will contribute to the baseline sum.

**NOTE 2**: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

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. Non-Nodal target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameter (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

Non-target lesions.
All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non- target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

**Methods for Evaluation of Measurable Disease**
All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than **30 days** before the beginning of the treatment.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. In the event the participant is intolerant to the contrast agent, an alternative imaging modality may be used. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

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.

**Response Criteria**

Evaluation of Target Lesions
Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum diameters. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of 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 5mm. The appearance of one or more new lesions is also considered progression.

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.
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 (<10mm short axis).

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): Unequivocal progression of existing non-target lesions or appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Evaluation of Time Point Response

| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluate | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD* | Yes or No | PD |
| Any | Any | Yes | PD |
| Not all evaluated | Non-PD | No | NE |

Note: If participants respond to treatment and are able to have their disease resected, the participant's response will be assessed prior to the surgery.

**Evaluation of Overall Response**
The best overall response is the best response recorded from the start of the treatment until the end of treatment (taking into account any requirement for confirmation). The participant's best overall response assignment will depend on the findings of target and non-target lesions, new lesions (as applicable) and confirmation criteria.

In non-randomized trials where response is the primary endpoint "best overall response" must be confirmed if CR or PR was achieved. A confirmatory assessment must be done ≥ 4 weeks after the previous assessment.

In the event that a confirmation is required, the "best overall response" is determined as listed below:

| Overall response at the first time point | Overall response at subsequent time point | Best overall Response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR* |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise, NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise, NE |
| NE | NE | NE |

*If a CR is met at the first time point, then any disease seen at a subsequent time point makes the disease PD at that point. Best response would depend on if the minimum duration for SD was met. In the case that CR was claimed when subsequent scans suggest small lesions were likely still present and that the participant did in fact have a PR at the first time point and not CR then the original CR should be changed to PR and the best response is PR.

**Duration of Response**

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

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

**Progression-Free Survival**
Progression-free survival (PFS) is defined as the duration of time from start of treatment until objective tumor progression or death. Participants who do not experience objective tumor progression or death during the evaluation period, or are lost to follow-up, will be censored.

**Overall Survival**
Overall survival is defined as the duration of time from start of treatment to death. Participants, who do not experience death during the evaluation period or who are lost to follow-up, will be censored.

# 10 STUDY AGENT

## 10.1 NIRAPARIB (MK-4827, ZEJULA) DRUG INFORMATION

For this study, NIRAPARIB is investigational

**PHARMACOLOGY**

Please refer to current Investigator Brochure or Package Insert.

**PHARMACOKINETICS**

Please refer to current Investigator Brochure or Package Insert

**ADVERSE EFFECTS**

Please refer to current Investigator Brochure or Package Insert, AND:

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

The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 367 patients receiving niraparib: neutropenia, palpitations, asthenia, neutrophil count decreased, dizziness, dysgeusia, dyspnea, cough and hypertension. The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients receiving niraparib: tachycardia, dry mouth, mucosal inflammation, white blood cell count decreased, aspartate aminotransferase increased, alanine aminotransferase increased and photosensitivity reaction.

**Pregnancy and Lactation:**

Please refer to current Investigator Brochure or Package Insert, AND:

**Breast Feeding**
Patients must not breast-feed from the first dose of niraparib and for **180** days following the final dose of niraparib.

**Drug Interactions:**

Please refer to current Investigator Brochure or Package Insert, AND:

**Foods**
Food does not significantly affect the absorption of niraparib; therefore, niraparib may be taken without regard to meals.

**Drug Interactions**
No formal drug interaction studies have been performed.

**Effect of Niraparib on Other Drugs (59):**

**Inhibition of CYPs (CYPA2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4)**
Neither niraparib nor the major primary metabolite M1 is an inhibitor of any drug-metabolizing CYP enzymes, namely CYPA2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. A clinically meaningful drug interaction via inhibition of CYPs is highly unlikely

**Induction of CYPs (CYPA2 and CYP3A4)**
Neither niraparib nor M1 is a CYP3A4 inducer. Niraparib weakly induces CYP1A2 in vitro, therefore, investigators are advised to use caution with the substrates for CYP1A2 with a narrow therapeutic range, i.e. theophylline and tizanidine. M1 is not a CYP1A2 inducer.

**Inhibition of Efflux Transporters (P-gp, BCRP, and BSEP)**
Niraparib is not an inhibitor of P-gp or BSEP. Niraparib is a weak inhibitor of BCRP in vitro. A clinically meaningful drug interaction via an inhibition of BCRP is unlikely. The major primary metabolite M1 does not appear to be an inhibitor of P-gp, BCRP, or

**Inhibition of Hepatic Uptake Transporters (OATP1B1, OATP1B3, and OCT1)**
Neither niraparib nor M1 is an inhibitor of OATP1B1, OATP1B3, or OCT1

**Inhibition of Renal Uptake Transporters (OAT1, OAT3, and OCT2)**
Neither niraparib nor M1 is an inhibitor of OAT1, OAT3, or OCT2.

**Effect of Other Drugs on Niraparib Substrate of CYPs**
Niraparib is a substrate of CEs in vivo. Oxidative metabolism of niraparib is minimal in vivo. No dose adjustment for niraparib is required when administered concomitantly with drugs known to inhibit or induce CYP enzymes. M1, the major circulating metabolite, is a substrate of UGTs in vivo.

**Substrate of Efflux Transporters (P-gp, BCRP, and BSEP)**
Niraparib is a substrate of P-gp and BCRP.
Niraparib is not a substrate of BSEP. The major primary metabolite M1 is not a substrate of P- gp, BCRP, or BSEP. No dose adjustment for niraparib is required when administered concomitantly with drugs known to be inhibitors of P-gp, BCRP, or BSEP. However, per manufacturer, TESARO, USE CAUTION when administered concomitantly with known inhibitors of P-gp.

**Substrate of Hepatic Uptake Transporters (OATP1B1, OATP1B3, and OCT1)**

Neither niraparib nor M1 is a substrate of OATP1B1, OATP1B3, or OCT1. No dose adjustment for niraparib is required when administered concomitantly with drugs known to be inhibitors of OATP1B1, OATP1B3, or OCT1.

**Substrate of Renal Uptake Transporters (OAT1, OAT3, and OCT2)**
Neither niraparib nor M1 is a substrate of OAT1, OAT3, or OCT2. No dose adjustment for niraparib is required when administered concomitantly with drugs known to be inhibitors of OAT1, OAT3, or OCT2.

**Granulocyte Colony-Stimulating Factor (GCSF)**
Prophylactic cytokine (Granulocyte Colony-Stimulating Factor [GCSF]) administration should not be given in the first cycle of the study, but may be administered in subsequent cycles according current American Society of Clinical Oncology (ASCO) guidelines.

**Other Anticancer Therapy**
No other anticancer therapy is permitted during the course of the study treatment for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to enrollment, per exclusion criteria above). If the patient discontinues study treatment, this restriction no longer applies, however the patient will remain enrolled in the study for the purpose of collecting subsequent outcomes. Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing > 20% of the bone marrow within 2 weeks of the first dose of study treatment and all during study treatment) is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.

The data on niraparib in combination with cytotoxic medicinal products are limited. Therefore, caution should be taken if niraparib is used in combination with other cytotoxic medicinal products.

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

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

## DOSING & ADMINISTRATION

See Method of Administration below and section with title TREATMENT PLAN

### Packaging, Labeling and Storage

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

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

### Stability

Information not provided.

**Route of Administration**

Oral

**Method of Administration**
Niraparib will be self-administered by the study participants with a full (8 oz or more) glass of water or juice, with OR without food.

The recommended dose of niraparib as monotherapy is three 100 mg capsules taken orally **once** daily, equivalent to a total daily dose of 300 mg,

**OR**

two 100 mg capsules taken orally once daily equivalent to a total daily dose of 200 mg (200mg dose is for participants whose baseline weight is <77 kg [169.756 lbs] or baseline platelet count is <150,000 µL).

Participants should take their study drug dose at approximately the same time each day.

Participants may consider taking their study drug dose at bedtime, as a possible method for managing nausea.

Niraparib treatment should be continued until disease progression or unacceptable toxicity.
If a participant vomits or misses a dose of niraparib, an additional dose should NOT be taken. The next dose should be taken at the regularly scheduled time.

**DRUG ORDERING AND ACCOUNTABILITY**

**Drug Ordering**
Niraparib will be ordered from funder TESARO and free of charge.

**Drug Handling and Accountability**
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the funder, TESARO. The study treatment accountability log includes information including a patient identifier, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as 'returned' and kept separate from the products not yet dispensed.

**Drug return and/or disposition instruction**
Used drug and remaining unused drug may be destroyed, according to the University of Kansas Investigational Drug Handling policy.

# 11 TREATMENT PLAN

Study Drug: Niraparib
Formulation: Tablet/Capsule
Dose: 300mg OR 200mg orally, once per day
Dose escalation will not be performed in this study.
Number of Doses per Cycle: 28 doses per cycle (once daily)
Cycle Duration (days): 28 days
Number of Cycles per Participant: Continue until disease progression
Combination Drugs or Agents: None

## 11.1.1 Duration Of Therapy

Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or per Investigator discretion if determined to be in the best interest of the participant.

## 11.1.2 Study Agent Accountability Procedures / Participant Compliance

Participants will be given a medication diary to record study drug doses.

Drug accountability will be noted at the completion of the trial. Participants will be instructed to keep all unused medication and empty pill bottles and return unused medication and empty pill bottles at ALL study visits. The site personnel must ensure the appropriate dose of each study drug is administered and drug accountability check is performed.

Unused study drug will be destroyed per KU IDS policy.

## 11.1.3 Dose Adjustments/Modifications/Delays

Any participant who receives treatment on this protocol will be evaluable for toxicity. Each participant will be assessed for the development of toxicity according to the Schedule of Events table.

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 and toxicity assessment. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

*http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm*

Information and links regarding CTCAE version 5.0 can be found at the CTEP website:

*https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50*

Dose adjustments should be made according to the system showing the greatest degree of toxicity.

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

Treatment must be interrupted for any nonhematologic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib. 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 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 the Recommended Dose Modifications for Adverse Reactions table below.

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 as outlined in the Niraparib Dose Modifications for Hematologic Toxicity table. 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.

**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) | NA |

**Niraparib Dose Modifications for Nonhematologic Adverse Reactions**

| **Abnormality** | **Intervention** |
|---|---|
| Non-hematologic CTCAE ≥ Grade 3 adverse reaction or adverse reaction persists despite treatment | Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction.<br>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. |

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

**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:<br>Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL.<br>Resume niraparib at same or reduced dose.<br>If platelet count is < 75,000/µL, resume niraparib at a reduced dose. |
| | Second occurrence:<br>Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL.<br>Resume niraparib at a reduced dose.<br>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.<br>Resume niraparib at a reduced dose.<br>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. |
| Hemoglobin ≤ 8 g/dL | Withhold niraparib for a maximum of 28 days and monitor blood counts until hemoglobin returns to ≥9 g/dL.<br>Resume niraparib at a reduced dose.<br>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. |
| Hematologic adverse reaction requiring transfusion | For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count.<br>Resume niraparib at a reduced dose. |
| 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.

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

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.

All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, will be recorded in the electronic case report form (eCRF).

#### 11.1.4 Nursing Staff Duty Implications

None

#### 11.1.5 Participant Access To Study Agent At Study Closure

The funder, TESARO, indicates they will not prospectively agree to provide study therapy after a participant experiences disease progression and therefore goes off study.

# 12 STUDY PROCEDURES AND SCHEDULE

## 12.1 DESCRIPTIVE SCHEDULE OF EVENTS

### 12.1.1 Screening

**Biomarker testing – required for participants**

Before signing consent for the main study, potential participants will be asked to consent to screening biomarker testing (unless biomarker information from previous testing is already known) of their tumor tissue in order to determine eligibility for the main study.

For the biomarker testing, potential participants should have availability of either formalin‐fixed, paraffin‐embedded archival tumor from the primary or recurrent cancer for integral biomarker analysis.

Archival tumor tissue will be processed by the KUCC correlative labs as described below.

If archival tumor tissue is not available, or if there is not enough tissue in the archival specimens for testing, potential participants will be asked to allow a new biopsy to obtain integral biomarker analysis.

For archival tumor tissue (this could be either from the biopsy tissue OR tissue gained in previous surgery), 10 unstained Superfrost Plus slides cut at a 10 micron thickness from the most representative and tumor cell enriched block along with the corresponding pathology report should be submitted. These slides will be used for H&E staining, and DNA extraction for mutational analysis using a custom next-generation sequencing (NGS) panel targeting the genes listed here: BRCA1/2, PALB2, ATM, NBN, ATR, BRIP1, IDH1/2, RAD51, RAD51B/C/D, RAD54L, CDK12, BARD1, FAM175A, BAP1, CHEK1/2, GEN1, MRE11A, XRCC2, SHFM1, FANCD2, FANCA, FANCC, FANCG, RPA1, ARID1A. The biomarker analyses for NGS will be performed through the Clinical Molecular Oncology Lab, a CAP-accredited, CLIA certified facility at KUMC (Director: Andrew K. Godwin). The H&E staining will be performed through the CLIA certified histopathology laboratory that is part of the BRCF at KUMC (Director Dr. Andrew Godwin).

**NOTIFICATION OF BIOMARKER TEST RESULTS**
If biomarker testing reveals a mutation that meets study eligibility criteria, then participants will be notified of the specific mutation.

The research team can tell the patients that the mutation found on the screening biomarker testing may have resulted in their development of pancreatic cancer, may impact their risk of developing other cancers, and also impact cancer risk in their family members. Further discussions regarding the role of germline testing and referral to genetic counseling will be deferred to the treating physician and patient. If the patient chooses to undergo germline testing to confirm the mutation then germline testing would be performed free of cost by the study and a report will be provided to the treating physician for further action. If the treating physician and patient choose to pursue genetic counseling and testing family members, if required, it would be considered a standard of care procedure.

Participants will be asked to consent to OPTIONAL storage of tissue from the screening biopsy for banking and future unspecified research.

NOTE: Participants whose biomarkers are already known at screening will also be offered an optional biopsy for tissue storage and future research.

**Blood draw for banking for future unspecified research -** OPTIONAL for participants.
See section with title *SAMPLE BANKING FOR FUTURE RESEARCH.*

### 12.1.2 Screening/Enrollment/Baseline

If the tests required at screening were performed as part of standard of care prior to signing consent for this study, the results from those tests are allowed in this study if the tests were completed within the timeframe listed below.

All screening procedures must be performed before they enroll on this study.

Screening tests listed below can be done up to **30 days** prior to registration ***unless otherwise stated***.

Tumor assessments will be performed throughout the study period and analyzed using Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.1 [57]) criteria.

Imaging (Computed tomography (CT) or MRI if CT contraindicated) scans will be performed every 8 weeks (WINDOW = + - 7 DAYS). The imaging modality used at screening must be used for that

participant throughout this study. In the event the participant is intolerant to the contrast agent, an alternative imaging modality may be used.

Toxicity assessments and management will be performed based on CTCAE ver. 5.0 guidelines as a standard of care.

**SCREENING VISIT**

**Informed Consent**

**Medical history**
Complete medical, surgical and oncology history are obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

**Demographics :** Demographic profile will include date of birth, gender, race, and zip code.

**Review participant eligibility criteria**
Review of eligibility criteria to ensure participant qualification for study entry.

**Review previous and concomitant medications**
All prior medication taken by the participant within 4 weeks before starting the study is to be recorded. Concomitant medications taken by the participant during the study are to be recorded up until 30-days after last study dose. If a reportable adverse event (see section with title *Adverse Events*) occurs within 30-days after last study dose, recording of concomitant medications should continue until resolution of the adverse event.

**Physical exam**
Exam will include vital signs, height and weight – height to be measured at screening/baseline only
Note: Vital signs include temperature, pulse, SpO2, blood pressure

**Performance status :** ECOG performance status

**Adverse event assessment :**
Baseline assessment via medical history, for determining later adverse events.

**Hematology**
Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential

**Serum chemistries**.
Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

**Additional Labs**
TSH with reflex T4, CA 19-9, CEA.

**Blood draw for banking for future unspecified research.** OPTIONAL for participants.
See section with title *SAMPLE BANKING FOR FUTURE RESEARCH.*

**Urinalysis**
Dipstick
If protein > 2+ then perform Creatinine/Protein ratio test

**Serum Pregnancy test (for females of child bearing potential)**
Completed with negative findings no more than 72 hours before study drug dosing

**Tumor assessment**
Imaging -- CT of chest, abdomen and pelvis (IV contrast will be used unless contraindicated)

If CT contraindicated – MRI will be allowed (IV contrast will be used unless contraindicated)

MRI or CT of brain (only in cases of brain metastatic disease. IV contrast will be used unless contraindicated)

The imaging modality used at screening must be used for that participant throughout this study. In the event the participant is intolerant to the contrast agent, an alternative imaging modality may be used.

### 12.1.3 Procedures During Treatment

**1 Cycle = 28 days**
**NOTE**: Serum pregnancy test for women of child-bearing potential to be done on Day 1 every 3 cycles (C1D1, C4D1, C7D1**,** etc.) and at End of Treatment visit

**Cycle 1 / DAY 1**

- Physical exam, vital signs and weight
- Review previous and concomitant medications
- ECOG
- Hematology - Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential (WINDOW: + / - 3 DAYS)
- Serum chemistries (Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin and tumor marker (CA 19-9) with CEA. (WINDOW: + / - 3 DAYS)
- TSH with reflex T4
- Tumor marker (CA19-9) and CEA
- Blood draw (3 tubes) for sample banking for future research – OPTIONAL for participants
- Circulating Tumor Cells (CTC) enumeration from whole blood, NOTE - One (whole blood in one EDTA tube per test) blood sample will be acquired before Niraparib administration. CTC analysis must be done <6 h from time of draw.
    - Circulating tumor cell (CTC) enumeration from blood performed at this time, according to the protocol presented in Witek et al.(66)
    - Circulating tumor cell (CTC) enumeration from blood will be performed by Dr. Steven A. Soper in the Liquid Biopsy Core at KUMC.
    - See section below with title *Correlative Studies (CTC enumeration)* for collection and processing details.

- Serum pregnancy test for women of child-bearing potential (if screening pregnancy test done more than 72 hours before first dose of study drug).
- Adverse Event Assessment
- Niraparib dosing (Oral) NOTE – Niraparib dosing is daily throughout every cycle.

- Pharmacokinetic (PK) Blood Samples
  - Pre-dose (baseline): A blood sample will be acquired no more than 30 minutes before niraparib administration
    **AND**
  - Post-dose:
    - ✓ Hour 3 (± 15 minutes)
    - ✓ Hour 24 (+ / - 1 hour) and BEFORE next dosing (this will be used to determine AUC 0-24 h)

**NOTE:** The exact time the participant takes the study drug after each pre-dose PK collection must be recorded to verify the timing of the PK samples.

**Cycle 1 / Day 8**

- Hematology - Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential (WINDOW: + / - 3 DAYS)
- Serum chemistries (Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin (WINDOW: + / - 3 DAYS)
- Niraparib dosing (Oral) NOTE – Niraparib dosing is daily throughout every cycle
- Review previous and concomitant medications
- Adverse Event Assessment

**Cycle 1 / Day 15**

- Physical exam, vital signs
- Review previous and concomitant medications
- Hematology (WINDOW: + / - 3 DAYS) Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential
- Serum chemistries (Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin (WINDOW: + / - 3 DAYS)
- Niraparib dosing (Oral) NOTE – Niraparib dosing is daily throughout every cycle
- Adverse Event Assessment

**Cycle 1 / Day 21**

- Review previous and concomitant medications
- Hematology (WINDOW: + / - 3 DAYS) Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential
- Serum chemistries (Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin (WINDOW: + / - 3 DAYS)
- Niraparib dosing (Oral) NOTE – Niraparib dosing is daily throughout every cycle
- Adverse Event Assessment

**Cycle 2 / DAY 1**

- Physical exam, vital signs and weight
- Review previous and concomitant medications
- ECOG
- Hematology - Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential (WINDOW: + / - 3 DAYS)
- Serum chemistries Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. (WINDOW: + / - 3 DAYS)
- TSH with reflex T4
- Tumor marker (CA19-9) and CEA
- Blood draw (two tubes) for sample banking for future research – OPTIONAL for participants
- Circulating Tumor Cells (CTC) enumeration from whole blood, NOTE - One (whole blood in one EDTA tube per test) blood sample will be acquired before Niraparib administration. CTC analysis must be done <6 h from time of draw.
    - Circulating tumor cell (CTC) enumeration from blood performed at this time, according to the protocol presented in Witek et al.(66)
    - Circulating tumor cell (CTC) enumeration from blood will be performed by Dr. Steven A. Soper in the Liquid Biopsy Core at KUMC.
    - See section below with title *Correlative Studies (CTC enumeration)* for collection and processing details.
- Adverse Event Assessment
- Niraparib dosing (Oral) – NOTE – Niraparib dosing is daily throughout every cycle.

- Pharmacokinetic (PK) Blood Samples

    - Pre-dose (baseline): A blood sample will be acquired no more than 30 minutes before niraparib administration
      **AND**
    - Post-dose:
        - ✓ Hour 3 (± 15 minutes)
        - ✓ Hour 24 (+ / - 1 hour) (this will be used to determine AUC 0-24 h). This PK sample to be collected before participant takes next dose of study drug.

**NOTE:** The exact time the participant takes the study drug after each pre-dose PK collection must be recorded to verify the timing of the PK samples.

**Cycle 2 / Day 22**

- Imaging scan (WINDOW: + / - 7 DAYS)
- Niraparib dosing (Oral) NOTE – Niraparib dosing is daily throughout every cycle
- Review previous and concomitant medications
- Adverse Event Assessment

**Cycle 3 / DAY 1**

- Physical exam, vital signs
- Review previous and concomitant medications
- ECOG
- Hematology - Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential (WINDOW: + / - 3 DAYS)
- Serum chemistries Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin (WINDOW: + / - 3 DAYS)
- TSH with reflex T4
- Tumor marker (CA19-9) and CEA
- Blood draw (two tubes) for sample banking for future research – OPTIONAL for participants
- Circulating Tumor Cells (CTC) enumeration from whole blood, NOTE - One (whole blood in one EDTA tube per test) blood sample will be acquired before Niraparib administration. CTC analysis must be done <6 h from time of draw.

  Circulating tumor cell (CTC) enumeration from blood performed at this time, according to the protocol presented in Witek et al.(66)

  Circulating tumor cell (CTC) enumeration from blood will be performed by Dr. Steven A. Soper in the Liquid Biopsy Core at KUMC.

  See section below with title *Correlative Studies (CTC enumeration)* for collection and processing details.
- Urinalysis - only if there was evidence at screening of proteinuria > 2 +, then do creatinine / protein ratio test
- Niraparib dosing (Oral) NOTE – Niraparib dosing is daily throughout every cycle
- Adverse Event Assessment
- Pharmacokinetic (PK) Blood Samples

  - Pre-dose ONLY: A blood sample will be acquired no more than 30 minutes before niraparib administration

**NOTE:** The exact time the participant takes the study drug after each pre-dose PK collection must be recorded to verify the timing of the PK samples.

**Cycle 4 / DAY 1**

- Physical exam, vital signs
- Review previous and concomitant medications
- ECOG
- Hematology - Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential (WINDOW: + / - 3 DAYS)
- Serum chemistries Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. (WINDOW: + / - 3 DAYS)
- TSH with reflex T4
- Tumor marker (CA19-9) and CEA
- Blood draw (two tubes) for sample banking for future research – OPTIONAL for participants

- Circulating Tumor Cells (CTC) enumeration from whole blood, NOTE - One (whole blood in one EDTA tube per test) blood sample will be acquired before Niraparib administration. CTC analysis must be done <6 h from time of draw.

  Circulating tumor cell (CTC) enumeration from blood performed at this time, according to the protocol presented in Witek et al.(66)

  Circulating tumor cell (CTC) enumeration from blood will be performed by Dr. Steven A. Soper in the Liquid Biopsy Core at KUMC.

  See section below with title *Correlative Studies (CTC enumeration)* for collection and processing details.
- Serum pregnancy test for women of child-bearing potential
- Urinalysis - only if there was evidence at screening of proteinuria > 2 +, then do creatinine / protein ratio test
- Adverse Event Assessment
- **Pre-dose only PK sampling to be done on DAY 1 OF EVERY CYCLE AFTER cycle 2**
  - Pre-dose ONLY: A blood sample will be acquired no more than 30 minutes before niraparib administration

**NOTE:** The exact time the participant takes the study drug after each pre-dose PK collection must be recorded to verify the timing of the PK samples.

- Niraparib dosing (Oral) – NOTE – Niraparib dosing is daily throughout every cycle
- Bone Marrow Biopsy/Aspiration
  For participants suspected of developing MDS/AML while on study, a bone marrow biopsy/aspirate will be performed per standard of care and delivered to the KU BRCF for processing and storage.

**All subsequent cycles / DAY 1**

- Physical exam, vital signs
- Review previous and concomitant medications
- ECOG
- Hematology - Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential (WINDOW: + / - 3 DAYS)
- Serum chemistries Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. (WINDOW: + / - 3 DAYS)
- TSH with reflex T4
- Tumor marker (CA19-9) and CEA
- Blood draw (two tubes) for sample banking for future research – OPTIONAL for participants
- Circulating Tumor Cells (CTC) enumeration from whole blood, NOTE - One (whole blood in one EDTA tube per test) blood sample will be acquired before Niraparib administration. CTC analysis must be done <6 h from time of draw.

  Circulating tumor cell (CTC) enumeration from blood performed at this time, according to the protocol presented in Witek et al.(66)

  Circulating tumor cell (CTC) enumeration from blood will be performed by Dr. Steven A. Soper in the Liquid Biopsy Core at KUMC.

See section below with title *Correlative Studies (CTC enumeration)* for collection and processing details.

- Urinalysis - only if there was evidence at screening of proteinuria > 2 +, then do creatinine / protein ratio test
- Adverse Event Assessment
- **Pre-dose only PK sampling to be done on DAY 1 OF EVERY CYCLE AFTER cycle 2**
  - Pre-dose ONLY: A blood sample will be acquired no more than 30 minutes before niraparib administration

**NOTE 1:** The exact time the participant takes the study drug after each pre-dose PK collection must be recorded to verify the timing of the PK samples.

- Niraparib dosing (Oral) – NOTE – Niraparib dosing is daily throughout every cycle
- Bone Marrow Biopsy/Aspiration
  For participants suspected of developing MDS/AML while on study, a bone marrow biopsy/aspirate will be performed per standard of care and delivered to the KU BRCF for processing and storage.

**NOTE 2**: Serum pregnancy test for women of child-bearing potential to be done on Day 1 every 3 cycles (C1D1, C4D1, **C7D1,** etc.) and at End of Treatment visit

### 12.1.4 End Of Treatment / Early Study Termination / Participant Study Withdrawal Visit

**End of Treatment (EOT) Visit**

- Physical exam, vital signs and weight
- Review previous and concomitant medications
- ECOG
- Hematology - Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential (WINDOW: + / - 3 DAYS)
- Serum chemistries Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. (WINDOW: + / - 3 DAYS)
- TSH with reflex T4
- Tumor tissue biopsy **and** blood draw (two tubes) for sample banking for future research – OPTIONAL for participants

See section with title *Correlative Studies (OR) SAMPLE BANKING FOR FUTURE RESEARCH*

- Circulating Tumor Cells (CTC) enumeration from whole blood One (whole blood in one EDTA tube per test) blood sample will be acquired before Niraparib administration. CTC analysis must be done <6 h from time of draw.

  Circulating tumor cell (CTC) enumeration from blood performed at this time, according to the protocol presented in Witek et al.(66)

  Circulating tumor cell (CTC) enumeration from blood will be performed by Dr. Steven A. Soper in the Liquid Biopsy Core at KUMC.

  See section below with title *Correlative Studies (CTC enumeration)* for collection and processing details.
- Serum pregnancy test for women of child-bearing potential
- Adverse Event Assessment

### 12.1.5 Safety Follow Up Visit

**30-60 Days after End of Treatment (EOT) Visit**

- Physical exam, vital signs and weight
- Review previous and concomitant medications
- ECOG
- Hematology - Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential (WINDOW: + / - 3 DAYS)
- Serum chemistries Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. (WINDOW: + / - 3 DAYS)
- Adverse Event Assessment

**90 Days after End of Treatment (EOT) Visit**

- Adverse Event Assessment **for pneumonitis, MDS/AML and secondary cancers only**

### 12.1.6 Post-Treatment Follow-Up Visit(s)

**For 5 years After Last Dose Of Study Drug:**
**Years 1 and 2**
**Every 6 months -**
Contact by telephone or certified mail to discover health status / survival
**Years 3 - 5**
**Annually**
Contact by telephone or certified mail to discover health status / survival

## 12.2 SCHEDULE OF EVENTS TABLES

### 12.2.1 SCREENING / BASELINE TO END OF CYCLE 3

| **Cycles = 28 Days** | | | **Cycle 1** | | | | **Cycle 2** | | | | **Cycle 3** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 |
| Required Studies | Screening | Eligibility Screening and Baseline **a** | **Day 1** | **Day 8** | **Days 15 and 21** | | **Day 1** | | | **Day 22** | **Day 1** | | | |
| Approximate Visit Time (in Hours) | | 7 | 5 | 3 | 3 | | 5 | | | 1-3 | 5 | | | |
| | | | | | | | | | | | | | | |
| Informed Consent | X | X | | | | | | | | | | | | |
| ** Biomarker Testing REQUIRED for participants | **X | | | | | | | | | | | | | |
| Medical History | | X | | | | | | | | | | | | |
| Demographics | | X | | | | | | | | | | | | |
| Review Eligibility Criteria | | X | | | | | | | | | | | | |
| Review Previous and Concomitant Medications | | X | X **g** | | | | X | | | X | X | | | |

| **Cycles = 28 Days** | | | **Cycle 1** | | | | **Cycle 2** | | | | **Cycle 3** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 |
| Required Studies | Screening | Eligibility Screening and Baseline **a** | **Day 1** | **Day 8** | **Days 15 and 21** | | **Day 1** | | | **Day 22** | **Day 1** | | | |
| Approximate Visit Time (in Hours) | | 7 | 5 | 3 | 3 | | 5 | | | 1-3 | 5 | | | |
| | | | | | | | | | | | | | | |
| Physical Exam Height, Weight, Vital Signs **i** | | X | X **g** | | X Day 15 | | X | | | | X | | | |
| ECOG Performance Status (PS)**c** WINDOW = +/- 7 DAYS | | X | X **g** | | | | X | | | | X | | | |
| Toxicity Notation (Adverse Events) | | X | X **g** | X | X | | X | | | X | X | | | |
| Participant Pill Diary Review **d** | | | At Every Visit | | | | | | | | | | | |
| **Labs** | | | | | | | | | | | | | | |
| Hematology**c** WINDOW = +/- 7 DAYS | | X | X **g** | X | X | | X | | | | X | | | |
| Serum Chemistry**c** WINDOW = +/- 7 DAYS | | X | X **g** | X | X | | X | | | | X | | | |
| TSH with reflex T4**c** WINDOW = +/- 7 DAYS | | X | X **g** | | | | X | | | | X | | | |

| **Cycles = 28 Days** | | | **Cycle 1** | | | | **Cycle 2** | | | | **Cycle 3** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 |
| Required Studies | Screening | Eligibility Screening and Baseline **a** | **Day 1** | **Day 8** | **Days 15 and 21** | | **Day 1** | | | **Day 22** | **Day 1** | | | |
| Approximate Visit Time (in Hours) | | 7 | 5 | 3 | 3 | | 5 | | | 1-3 | 5 | | | |
| | | | | | | | | | | | | | | |
| Tumor markers (CA19-9 and CEA)**c** WINDOW = +/- 7 DAYS | | X | X **g** | | | | X | | | | X | | | |
| Urinalysis**h,c** WINDOW = +/- 7 DAYS | | X | | | | | | | | | | | | |
| Circulating Tumor Cells (CTC) test **n** REQUIRED for participants | | | X **g** | | | | X | | | | X | | | |
| **Serum** Pregnancy Test **b** | | X | X**o** | | | | | | | | | | | |
| **Radiology Disease Assessment** **f** | | | | | | | | | | | | | | |
| Imaging scan WINDOW = +/- 7 DAYS **f,p** | | X | | | | | | | | X | | | | |

| **Cycles = 28 Days** | | | **Cycle 1** | | | | **Cycle 2** | | | | **Cycle 3** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 |
| Required Studies | Screening | Eligibility Screening and Baseline **a** | **Day 1** | **Day 8** | **Days 15 and 21** | | **Day 1** | | | **Day 22** | **Day 1** | | | |
| Approximate Visit Time (in Hours) | | 7 | 5 | 3 | 3 | | 5 | | | 1-3 | 5 | | | |
| | | | | | | | | | | | | | | |
| **Treatment** | | | | | | | | | | | | | | |
| Niraparib Dosing Once Daily **d** | | | Once Daily For 28 Days | | | | Once Daily For 28 Days | | | | Once Daily For 28 Days | | | |
| Blood sample collection for correlative studies **(PK)** REQUIRED for participants **k,L** | | | X D1 **k** | | | | X D1 **k** | | | | X D1 **L** | | | |
| Blood or Tumor Tissue collection for banking and future unspecified research **q** (OPTIONAL for participants) | X (Tumor tissue and Blood) | X (Blood only) | X (Blood only) | | | | X (Blood only) | | | | X (Blood only) | | | |

| **Cycles = 28 Days** | | | **Cycle 1** | | | | **Cycle 2** | | | | **Cycle 3** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 | Days 1 - 7 | Days 8 - 14 | Days 15 - 21 | Days 22 - 28 |
| Required Studies | Screening | Eligibility Screening and Baseline **a** | **Day 1** | **Day 8** | **Days 15 and 21** | | **Day 1** | | | **Day 22** | **Day 1** | | | |
| Approximate Visit Time (in Hours) | | 7 | 5 | 3 | 3 | | 5 | | | 1-3 | 5 | | | |
| | | | | | | | | | | | | | | |
| Bone marrow aspirate and biopsy per standard of care, if MDS/AML suspected **m** | | | X**m** | | | | | | | | | | | |

**** Before signing consent for the main study, potential participants will be asked to consent to screening biomarker testing (unless biomarker information from previous testing is already known) of their tumor tissue in order to determine eligibility for the main study.

For the biomarker testing, potential participants should have availability of either formalin‐fixed, paraffin‐embedded archival tumor from the primary or recurrent cancer for integral biomarker analysis.

Archival tumor tissue will be processed by the KUCC correlative labs as described below.

If archival tumor tissue is not available, or if there is not enough tissue in the archival specimens for testing, potential participants will be asked to allow a new biopsy to obtain integral biomarker analysis.

For archival tumor tissue (this could be either from the biopsy tissue OR tissue gained in previous surgery), 10 unstained Superfrost Plus slides cut at a 10 micron thickness from the most representative and tumor cell enriched block along with the corresponding pathology report should be submitted. These slides will be used for H&E staining, and DNA extraction for mutational analysis using a custom next-generation sequencing (NGS) panel targeting the genes listed here: BRCA1/2, PALB2, ATM, NBN, ATR, BRIP1, IDH1/2, RAD51, RAD51B/C/D, RAD54L, CDK12, BARD1, FAM175A, BAP1, CHEK1/2, GEN1, MRE11A, XRCC2, SHFM1, FANCD2, FANCA, FANCC, FANCG, RPA1, ARID1A. The biomarker analyses for NGS will be performed through the Clinical Molecular Oncology Lab, a CAP-accredited, CLIA certified facility at KUMC (Director: Andrew K. Godwin). The H&E staining will be performed through the CLIA certified histopathology laboratory that is part of the BRCF at KUMC (Director Dr. Andrew Godwin).

Biomarker analysis will be done by KU Clinical Molecular Oncology Laboratory (CMOL).

**NOTIFICATION OF BIOMARKER TEST RESULTS**
If biomarker testing reveals a mutation that meets study eligibility criteria, then participants will be notified of the specific mutation.

The research team can tell the patients that the mutation found on the screening biomarker testing may have resulted in their development of pancreatic cancer, may impact their risk of developing other cancers, and also impact cancer risk in their family members. Further discussions regarding the role of germline testing and referral to genetic counseling will be deferred to the treating physician and patient. If the patient chooses to undergo germline testing to confirm the mutation then germline testing would be performed free of cost by the study and a report will be provided to the treating physician for further action. If the treating physician and patient choose to pursue genetic counseling and testing family members, if required, it would be considered a standard of care procedure.

Participants will be asked to consent to OPTIONAL storage of tissue from the screening biopsy for banking and future unspecified research.

NOTE: Participants whose biomarkers are already known at screening will also be offered an optional biopsy for tissue storage and future research.

**Blood draw for banking for future unspecified research -** OPTIONAL for participants.
See section with title *SAMPLE BANKING FOR FUTURE RESEARCH.*

- **a** Within 30 days of registration/enrollment during potential participants' first line of chemotherapy treatment – EXCEPT for biomarker testing
- **b** Serum pregnancy test for women of child-bearing potential (if screening pregnancy test done more than 72 hours before first dose of study drug.
- **c** WINDOW = +/- 7 DAYS

**d** Pill Diary is a separate, stand-alone document

**e** XX

**f** Every 8 weeks (WINDOW = +/- 7 DAYS)

**g** Cycle 1 can use screening labs if results are within 7 DAYS of start of therapy

**h** After enrollment screening visit, urinalysis only if there was evidence at screening of proteinuria > 2 +, then obtain protein / creatinine ratio.

**i** Vital signs include temperature, pulse, SpO2, and blood pressure. Height is to be measured at screening/baseline only.

**j** IV contrast will be used unless contraindicated. In the event the participant is intolerant to the contrast agent, an alternative imaging modality may be used.

**k** Pharmacokinetic (PK) Blood Samples to be performed on C1D1 and C2D1 as below.

- Pre-dose (baseline): A blood sample will be acquired no more than 30 minutes before niraparib administration
  **AND**
- Post-dose:
  - ✓ Hour 3 (± 15 minutes)
  - ✓ Hour 24 (+ / - 1 hour) (this will be used to determine AUC 0-24 h). This PK sample to be collected before participant takes next dose of study drug.

**l** **After Cycle 2 -- Pre-dose only PK sampling to be done on Day 1 of every cycle after cycle 2**

- Pre-dose ONLY: A blood sample will be acquired no more than 30 minutes before niraparib administration

**NOTE:** The exact time the participant takes the study drug before each pre-dose PK collection must be recorded to verify the timing of the PK samples.

**m** Bone marrow biopsy/aspiration should be performed per standard of care if a patient is suspected to develop MDS/AML and delivered to the KU BRCF for processing and storage.

**n** One (whole blood in one EDTA tube per test) blood sample will be acquired before Niraparib administration. CTC analysis must be done <6 h from time of draw.

Circulating tumor cell (CTC) enumeration from blood performed at this time, according to the protocol presented in Witek et al.(66)

Circulating tumor cell (CTC) enumeration from blood will be performed by Dr. Steven A. Soper in the Liquid Biopsy Core at KUMC.

See section below with title *Correlative Studies (CTC enumeration)* for collection and processing details.

- **o** Serum pregnancy test to be done every 3 cycles (C1D1, C4D1, C7D1**,** etc.) and at End of Treatment visit for women of child-bearing potential (at cycle 1, need only be repeated if screening pregnancy test done more than 72 hours before first dose of study drug).
- **p** Imaging -- CT of chest, abdomen and pelvis (IV contrast will be used unless contraindicated).

If CT contraindicated – MRI will be allowed (IV contrast will be used unless contraindicated). MRI or CT of brain (only in cases of brain metastatic disease. IV contrast will be used unless contraindicated). The imaging modality used at screening must be used for that participant throughout this study. In the event the participant is intolerant to the contrast agent, an alternative imaging modality may be used.

- **q** OPTIONAL Blood draws for storage and future research: C1D1 = 3 tubes. All other cycles, D1 = 2 tubes.

### 12.2.2 CYCLE 4 TO END OF TREATMENT AND FOLLOW UP

| | **Cycle 4** | | | | **Cycles 5 Onward** | | | | **End of Treatment (EOT)** | **Safety Follow Up** | | **Follow Up for MDS / AML .** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Required Studies | Days 1 to 7 | Days 8 to 14 | Days 15 to 21 | Days 22 to 28 | Days 1 to 7 | Days 8 to 14 | Days 15 to 21 | Days 22 to 28 | | **30 - 60 Days after EOT** | **90 Days after EOT** | **Years 1 – 2 After EOT Every 6 months** | **Years 3 – 5 after EOT Annually** |
| | **Day 1** | | | | **Day 1** | | | | | | | | |
| Approximate Visit Time (In Hours) | 5-7 | | | 3-5 | 5-7 | | | 3-5 | 5-7 | 1-3 | 1-3 | | |
| | | | | | | | | | | | | | |
| Review Previous and Concomitant Medications[a] | X | | | | X | | | | X | X | | | |
| Physical Exam – Weight, Vital Signs **a,d** | X | | | | X | | | | X | X | | | |
| ECOG Performance Status (PS) WINDOW = +/- 7 DAYS | X | | | | X | | | | X | X | | | |
| Toxicity Notation (Adverse Events)[a,m,n] | X | | | | X | | | | X | X | X[m] | | |
| Participant Pill Diary Review [b] | At every visit | | | | | | | | | | | | |

| | **Cycle 4** | | | | **Cycles 5 Onward** | | | | **End of Treatment (EOT)** | **Safety Follow Up** | | **Follow Up for MDS / AML .** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Required Studies | Days 1 to 7 | Days 8 to 14 | Days 15 to 21 | Days 22 to 28 | Days 1 to 7 | Days 8 to 14 | Days 15 to 21 | Days 22 to 28 | | **30 - 60 Days after EOT** | **90 Days after EOT** | **Years 1 – 2 After EOT Every 6 months** | **Years 3 – 5 after EOT Annually** |
| | **Day 1** | | | | **Day 1** | | | | | | | | |
| Approximate Visit Time (In Hours) | 5-7 | | | 3-5 | 5-7 | | | 3-5 | 5-7 | 1-3 | 1-3 | | |
| | | | | | | | | | | | | | |
| **Labs** | | | | | | | | | | | | | |
| Hematology[a] WINDOW = +/- 7 DAYS | X | | | | X | | | | X | X | | | |
| Serum Chemistry[a] WINDOW = +/- 7 DAYS | X | | | | X | | | | X | X | | | |
| TSH with reflex T4[a] WINDOW = +/- 7 DAYS | X | | | | X | | | | X | | | | |
| Tumor markers (CA19-9 and CEA)[a] WINDOW = +/- 7 DAYS | X | | | | X | | | | | | | | |
| **Serum** Pregnancy Test[l] | X | | | | | | | | X | | | | |
| Urinalysis [a,c] WINDOW = +/- 7 DAYS | X | | | | X | | | | X | | | | |
| Circulating Tumor Cells (**CTC**) test [h] REQUIRED for participants | X | | | | X | | | | X | | | | |

| | **Cycle 4** | | | | **Cycles 5 Onward** | | | | **End of Treatment (EOT)** | **Safety Follow Up** | | **Follow Up for MDS / AML .** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Required Studies | Days 1 to 7 | Days 8 to 14 | Days 15 to 21 | Days 22 to 28 | Days 1 to 7 | Days 8 to 14 | Days 15 to 21 | Days 22 to 28 | | **30 - 60 Days after EOT** | **90 Days after EOT** | **Years 1 – 2 After EOT Every 6 months** | **Years 3 – 5 after EOT Annually** |
| | **Day 1** | | | | **Day 1** | | | | | | | | |
| Approximate Visit Time (In Hours) | 5-7 | | | 3-5 | 5-7 | | | 3-5 | 5-7 | 1-3 | 1-3 | | |
| | | | | | | | | | | | | | |
| **Radiology Disease Assessments[f]** | | | | | | | | | | | | | |
| Imaging scan[a,e,i,J] WINDOW = +/- 7 DAYS | | | | X | | | | X[i] | X | | | | |
| **Treatment** | | | | | | | | | | | | | |
| Niraparib Dosing Once Daily | Once Daily For 28 Days | | | | Once Daily For 28 Days | | | | | | | | |
| Blood sample collection for correlative studies **(PK)** REQUIRED for participants[f] | X D1[f] | | | | X D1[f] | | | | | | | | |

| | **Cycle 4** | | | | **Cycles 5 Onward** | | | | **End of Treatment (EOT)** | **Safety Follow Up** | | **Follow Up for MDS / AML .** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Required Studies | Days 1 to 7 | Days 8 to 14 | Days 15 to 21 | Days 22 to 28 | Days 1 to 7 | Days 8 to 14 | Days 15 to 21 | Days 22 to 28 | | **30 - 60 Days after EOT** | **90 Days after EOT** | **Years 1 – 2 After EOT Every 6 months** | **Years 3 – 5 after EOT Annually** |
| | **Day 1** | | | | **Day 1** | | | | | | | | |
| Approximate Visit Time (In Hours) | 5-7 | | | 3-5 | 5-7 | | | 3-5 | 5-7 | 1-3 | 1-3 | | |
| | | | | | | | | | | | | | |
| Blood or Tumor Tissue collection for banking and unspecified future research[n] (OPTIONAL for participants) | X (Blood only) | | | | X (Blood only) | | | | X (Biopsy and / or blood draw) | | | | |
| Bone marrow aspirate and biopsy[g] | X[g] | | | | | | | | | | | | |
| Contact by telephone or certified mail to discover health status / survival | | | | | | | | | | | | X | X |

**a** WINDOW = +/- 7 DAYS
**b** Pill diary is a separate, stand-alone document
**c** If there was evidence at screening of proteinuria > 2 +, then obtain protein / creatinine ratio.
**d** Vital signs include temperature, pulse, SpO2, and blood pressure.
**e** Every 8 weeks - Imaging -- CT of chest, abdomen and pelvis (IV contrast will be used unless contraindicated).

If CT contraindicated – MRI will be allowed (IV contrast will be used unless contraindicated). MRI or CT of brain (only in cases of brain metastatic disease. IV contrast will be used unless contraindicated). The imaging modality used at screening must be used for that participant throughout this study. In the event the participant is intolerant to the contrast agent, an alternative imaging modality may be used.

**f** **After Cycle 2 -- <u>Pre-dose only PK sampling to be done on Day 1 of every cycle after cycle 2</u>**

- Pre-dose ONLY: A blood sample will be acquired no more than 30 minutes before niraparib administration

**NOTE:** The exact time the participant takes the study drug <u>before each pre-dose PK collection</u> must be recorded to verify the timing of the PK samples

**g** Bone marrow biopsy/aspiration should be performed per standard of care if a patient is suspected to develop MDS/AML and delivered to the KU BRCF for processing and storage.

**h** One (whole blood in one EDTA tube per test) blood sample will be acquired before Niraparib administration. CTC analysis must be done <6 h from time of draw.

Circulating tumor cell (CTC) enumeration from blood performed at this time, according to the protocol presented in Witek et al.(66)

Circulating tumor cell (CTC) enumeration from blood will be performed by Dr. Steven A. Soper in the Liquid Biopsy Core at KUMC.

See section below with title *Correlative Studies (CTC enumeration)* for collection and processing details.

**i** Patients continue to have imaging scans performed every 8 weeks

**j** For patients without documented disease progression on trial: Require Imaging scan (WINDOW: + / - 7 DAYS) until progressive disease

**k** **IF** hematology labs indicate MDS/AML suspected, the following standard of care assessments for survival and/or development of MDS/AML will be done per PI discretion:

- CBC with diff
- Peripheral smear
- Bone Marrow Biopsy

**l** Serum pregnancy test to be done every 3 cycles (C1D1, C4D1, C7D1**,** etc.) 72 hours before first dose of study drug, and at End of Treatment visit.

**m** Adverse event assessment at 90 days after EOT will be for pneumonitis, MDS/AML and secondary cancers only

**n** OPTIONAL Blood draws for storage and future research: 2 tubes

# 13 CORRELATIVE STUDIES AND SAMPLE BANKING FOR FUTURE RESEARCH

## 13.1 Correlative Studies (Pharmacokinetics) – REQUIRED for Participants

### 13.1.1 Pharmacokinetics

Sampling and analysis of niraparib plasma concentrations will be performed to verify individual patient drug exposure. Whole blood will be collected in tubes with EDTA as the anticoagulant as follows:

**C1D1 and C2D1**

- Pre-dose (baseline): A blood sample will be acquired no more than 30 minutes before niraparib administration
  **AND**
- Post-dose:
  - ✓ Hour 3 (± 15 minutes)
  - ✓ Hour 24 (+ / - 1 hour) (this will be used to determine AUC 0-24 h). This PK sample to be collected before participant takes next dose of study drug.

**NOTE:** The exact time the participant takes the study drug before each pre-dose PK collection must be recorded to verify the timing of the PK samples.

**After Cycle 2 -- Pre-dose only PK sampling to be done on Day 1 of every cycle after cycle 2**

- Pharmacokinetic (PK) Blood Samples
  - Pre-dose **ONLY**: A blood sample will be acquired no more than 30 minutes before niraparib administration

**NOTE:** The exact time the participant takes the study drug before each pre-dose PK collection must be recorded to verify the timing of the PK samples.

These time points will provide data for determination of Cmax, tmax, AUC (0-24 hrs), and trough plasma concentration values both for first dose and at steady-state.

**Assays and sample processing to be completed by Charles River Labs/Agilux per funder requirements. See separate laboratory manual for shipping and assay details.**
The samples will be labeled with the participant's de-identified study number and collection date.

A population PK modeling approach may be used to describe plasma concentrations of niraparib and its metabolite in patients. If appropriate, covariates will be evaluated to determine if they contribute to differences in the PK estimates among individuals

## 13.2 Correlative Studies (CTC enumeration)– REQUIRED for participants

Circulating Tumor Cells subpopulations (mesenchymal and epithelial) will be enumerated directly from whole blood according the protocol in Witek *et. al*.(66) CTC will be enumerated on the first day of each treatment cycle, on the day of imaging (CT or MRI) scan, EOT, and post treatment (every ~8 weeks). The CTC burden changes will be correlated with treatment progression and PFS will be established.

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').

Blood samples for CTC are to be sent to:

The University of Kansas Cancer Center
Wahl Hall East (WHE)
Room 1020
3901 Rainbow Blvd
Kansas City, KS 66160

**Attn**: Nick Larkey 253-592-9195
*nlarkey@kumc.edu*

or

Maggie Witek 225-937-5987
*mwitek@ku.edu*

KUCC correlative labs will oversee the CTC blood collection and shipping to the KUMC Witek lab.

## 13.3 Sample Banking for Future Research – BANKING is OPTIONAL for participants

With participant consent only, tumor tissue and blood samples will be collected at times listed in the Schedule of Events for storage and future, unspecified research.

## 13.4 Sample Collection Instructions for Future Research

Surgically resected tumor material will be delivered to the BRCF at KU for standard processing and storage. Blood Samples will be collected at the time points listed in the Schedule of Events Table and section with title DESCRIPTIVE SCHEDULE OF EVENTS. For each patient at each collection time point 2 x 10 mL red-top, and 2 x 10 mL lavender-top tube EDTA (about 7.5 mL of whole blood per tube) will be collected, processed and cryogenically stored for future correlative studies. In addition, the buffy coat layer will be collected and cryopreserved from the plasma samples.

For those participants suspected of developing MDS/AML while on study, a bone marrow biopsy/aspirate will be collected per standard of care and delivered to the BRCF for processing and storage.

## 13.5 Sample Banking for Future Research (Optional for Participants)

After collection by **clinic nurse or phlebotomist** and preparation by **laboratory personnel,** the samples will be labeled with the participant's de-identified study number and collection date and delivered for storage for future research to:

The University of Kansas Cancer Center
Biospecimen Repository Core Facility (BRCF)
G001 Wahl Hall West
Mailstop 1027
3901 Rainbow Boulevard
Kansas City, KS 66160
**LABORATORY PHONE: 913-588-1718**
Phone: 913-588-4766
Fax: 913-588-4198
http://www.kumc.edu/school-of-medicine/biospecimen.html

under the direction of:

Dr. Andrew Godwin, PhD
The University of Kansas Cancer Center
Director of Molecular Oncology
4005B Wahl Hall East
Mailstop 3040
3901 Rainbow Boulevard
Kansas City, KS 66160
Phone: 913-945-6373
Fax: 913-945-6327
*agodwin@kumc.edu*

## 13.6 Sample Preparation, Handling, And Storage

**Tumor Tissue for Screening Biomarker Analysis**
Tumor tissue will be collected and the tissue will be processed in the CLIA Certified histopathology laboratory that is part of the BRCF. Resected tissue samples will be processed on Sakura VIP2000 automated Tissue Processor, embedded on Sakura Tissue Tek Embedding Center, sectioned on fully automated rotary Leica RM2255 Microtome. Standard H&E staining will be performed manually, while specific IHC staining will be performed on Automated Intellipath FLX stainer, BioCare, by a board certified Histotech (Tara Meyer, HT(ASCP)). A board certified pathologist (Dr. Rashna Madan, Assistant Director, BRCF) will review the representative sections and record tumor cellularity prior to molecular analyses and after IHC staining.

After processing, specimens will be delivered to the KUMC Clinical Molecular Oncology Laboratory (CMOL) for biomarker analysis at the address below:

The University of Kansas Medical Center
Clinical Molecular Oncology Lab (CMOL)
4005 Wahl Hall East
Mailstop 3040
3901 Rainbow Boulevard
Kansas City, KS 66160
**LABORATORY PHONE: 913-945-6391**
Fax: 913-945-6373

**Post-treatment Tumor Tissue for Future Research – Processing and Storage**
Surgically resected post treatment tumor samples will be delivered fresh to the BRCF. Tissue will be frozen and stored in -80 °C freezer for future research

**Bone marrow biopsy/aspirate**
Specimen from any bone marrow biopsy/aspirate will be delivered to the BRCF for processing.

**Blood Samples for Future Research - Serum Separation Procedure**

1. **Label Cryogenic vials**. Label three 1.5 mL screw-cap cryovials with the protocol number, the participant's de-identified study number, collection date (mm/dd/yyyy), and specimen type.
2. **Draw Blood**. Draw blood into **two red-top** Vacutainer® tube (no additives), until vacuum is exhausted. Allow blood to clot in an upright position at room temperature for 30 minutes before centrifugation.
3. **Centrifuge Blood.** Place serum vacutainer/blood tube into centrifuge with applicable balance. Set centrifuge to 1,300 x g for 10 minutes at 4 °C (if a refrigerated centrifuge is unavailable, process at 1000 x g at room temperature for 10 minutes).
4. **Aliquot Serum**. After centrifugation, carefully move blood tubes from centrifuge to a biological safety cabinet. Remove the cap from the blood tube and aliquot the serum evenly with a pipette into the appropriately labeled screw-cap cryovials. Fill each cryovial with 1.0 mL of serum. Then, cap the cryovials securely. This process should be completed within 1 h of centrifugation. ***Caution: Do not contaminate serum with red blood cells. This can be accomplished by keeping the pipette above the red blood cell layer and leaving a small amount of serum in the tube.***

5. **Freeze Serum**. After obtaining serum, immediately place cryovials into appropriate storage container in an upright position. Then, place into -80 °C freezer. Samples to be maintained -80 °C until ready for use. Do not thaw unless instructed.

**Blood Samples for Future Research - Plasma Separation Procedure**

1. **Label Cryogenic vials**. Label eight 1.5 mL screw-cap cryovials with the protocol number, the participant's study number, collection date (mm/dd/yyyy), and specimen type.
2. **Draw Blood**. Draw blood into **two lavender (EDTA) top** Vacutainer® tube, respectively, until the vacuum is exhausted. Then, gently invert tubes 5-10 times to ensure mixing of anti-coagulant.
3. **Centrifuge Blood**. Place EDTA vacutainer/blood tubes into centrifuge with applicable balance. Set centrifuge to 3,500 x g at 4˚C for 10 min (if a refrigerated centrifuge is unavailable, process at 1000 x g at room temperature for 15 minutes). This should be done with an acceleration of 9 and a deceleration of 0. If centrifugation cannot be immediately conducted, place in a 4˚C refrigerator and complete within 4 hours.
4. **Aliquot Plasma**. After centrifugation, carefully move blood tubes from centrifuge into a biological safety hood, taking extra care not to disturb component layers. In the safety hood, ease off the caps from a single specimen and, with a pipette, carefully aliquot 1.0 mL of the plasma component and transfer to respective/appropriately labeled cryovial. Then, cap cryovials securely. Pay close attention not to disturb the buffy coat layer just below the plasma, which will be processed in a separate procedure.
5. **Freeze Plasma**. After obtaining plasma, immediately place cryovials into appropriate storage container in an upright position. Then, place into -80 °C freezer. Samples to be maintained -80 °C until ready for use. Do not thaw unless instructed.

**Blood Samples for Future Research - Buffy Coat Procedure**

1. **Label Cryogenic vials.** Label two 1.5 mL screw-cap cryovials with the protocol number, the participant's study number, collection date (mm/dd/yyyy), and specimen type.
2. **Aliquot Buffy Coat**. After carefully removing plasma (done in previously outlined plasma procurement) from respective vacutainer tube, using a pipette, aliquot 1.0 mL of buffy boat into respective/appropriately labeled cryovial. Cap the cryovials securely.
3. **Freeze Buffy Coat.** After obtaining buffy coat, immediately place cryovials into appropriate storage container in an upright position. Place into -80 °C freezer. Samples to be maintained -80 °C until ready for use. Do not thaw unless instructed.

**Instructions for shipment of samples:**

For participants seen at the KU Cancer Center:
Staff from the Correlative Laboratory will receive samples from the clinic nurse and transfer them to the courier for transport to the BRCF.

For participants seen at the community sites:
For participants seen at community sites, samples will be given to the courier for transport to the BRCF.

Samples will be stored indefinitely or until they are used up. If future use is withdrawn by the participant, best efforts will be made to stop any additional studies and to destroy the samples.

The Sponsor – investigator of this trial will be responsible for reviewing and approving requests for clinical samples from potential research collaborators outside of the University of Kansas. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states samples will only be released for use in disclosed research. Any data obtained from the use of clinical sample will be the property of the University of Kansas for publication and any licensing agreement will be strictly adhered to.

The link to clinically annotated data for each participant's de-identified study number and collection date will be maintained on the secure, password protected KUMC computer server and the Sponsor-Investigator will not disclose this to future, potential research collaborators.

The samples, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the participant that there is the potential for financial gain by the University of Kansas, the investigator or a collaborating researcher or entity.

### 13.7 Future Use Of Stored Specimens

Tumor tissue and blood including DNA will be collected as outlined in the Schedule of Events Table. Specimens will be stored at the KU BRCF for future unspecified research.

## 14 STATISTICAL CONSIDERATIONS

### 14.1 Randomization

No randomization used in this study

### 14.2 Sample Size Justification

Simon's minimax two-stage design (67) will be used. The null hypothesis is that the true response rate is 0.05 will be tested against a one-sided alternative of 25%. In the first stage, 11 patients will be accrued. If there are 0 responses in these 11 patients, the study will be stopped. Otherwise, 7 additional patients will be accrued for a total of 18. The null hypothesis will be rejected if 3 or more responses are observed in 18 patients. This design yields a type I error rate of 0.10 and power of 0.85 when the true response rate is 25%.

## 14.3 Description Of Statistical Methods

### 14.3.1 General Approach

This is a phase II study aimed at assessing antitumor efficacy of Niraparib using Objective Response Rate in metastatic pancreatic cancers harboring DNA repair defects.

18 patients will be accrued over 24 months. Each patient will be followed for 12 months. Hence estimated total study period is 36 months to evaluate study objectives.

Simon's two stage design will be used to assess the primary objective. Time to event endpoints will be summarized with Kaplan-Meier curves and estimation of medians with 95% confidence intervals.

Based on the RECIST criteria, the responses will be categorized into complete response, partial response, progressive disease and stable disease and will be summarized in the table. Overall toxicity will be summarized in table by type and severity.
Adverse event terms will be coded using the current version of the Medical Dictionary and will be summarized for all treated patients. Incidence of AEs occurring during the study will be summarized by system organ class and preferred term. Adverse events will also be summarized by causality and grade. Serious adverse events will be listed separately. Descriptive summary statistics will be used to summarize changes over time in laboratory values, vital signs, and physical examination findings for all treated patients. Laboratory parameter changes will be described using shift tables, relative to CTCAE (v.5.0).

The percentage of participants having progression free survival at several follow-up time points will be tabulated and the results will be displayed with line or bar graph.

### 14.3.2 Analysis Of Primary Objective

Based on the Simon two-stage design, the null hypothesis will be rejected if 3 or more responses are observed in 18 patients, and we will conclude the niraparib is sufficiently active for further study in this patient population. If the study stops at the end of stage 1, or fewer than 3 responses are observed at the end of stage 2, we will fail to reject the null and conclude that niraparib is not sufficiently active in this patient population to pursue further. The response rate with 95% confidence interval will be estimated using the approach described by Koyama (63).

### 14.3.3 Analysis Of Secondary Objective(s)

Time to event endpoints will be summarized with Kaplan-Meier curves and estimation of medians with 95% confidence intervals. Adverse events will be tabulated by type and grade. Disease control rate at 8 weeks will be estimated as a proportion with its 95% confidence interval.

## 14.4 Unblinding Rules

None

### 14.5 Study Stopping Rules

With the exceptions of either fatigue, or of hypertension that can be treated with anti-hypertensives, if a participant experiences a CTCAE grade 3 – 5 toxicity which is possibly related to study treatment, first, dose reductions/delays described earlier in this protocol will be utilized. If necessary, study will be suspended pending data safety monitoring review to determine if study should continue.

Another stopping criterion is based on Simon's two-stage design (Simon, 1989).
In the first stage, 11 patients will be accrued. If there are 0 responses in these 11 patients, the study will be stopped.

## 15 PARTICIPANT REGISTRATION PROCEDURES

**General Guidelines**
Institutions will register eligible participants through the KUCC Clinical Research Office central registration process. Registration must occur prior to the initiation of therapy, with treatment assignment (for both randomized and non-randomized studies) provided by KUCC. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

The completed source documentation provided for eligibility verification and registration must be kept in the participant binder for monitoring purposes and documentation of participant eligibility.

Issues that would cause treatment delays should be discussed with the Sponsor- Investigator. If a participant does not receive protocol therapy following registration, notify the KU Cancer Center Project Director or designee so that the participant's status can be changed in the CRIS system.

**Registration Process for KUCC and Other Participating Centers**
The Coordinating Center (KUCC), specifically the Project Director or designee is accessible for registration Monday through Friday from 8:00 AM to 5:00 PM Central Time.

**The registration procedures are as follows:**

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments. **NOTE** – if tests required at screening were performed as part of standard of care prior to signing consent for this study, the results from those tests are allowed in this study IF those tests were performed within the timeframe listed in the section of this protocol with title *DESCRIPTIVE SCHEDULE OF EVENTS.*

2. Complete the appropriate baseline demographic information in CRIS and any required registration forms using the eligibility assessment documented in the participant's medical/research record. To be eligible for registration to the study, the participant must meet each inclusion and none of the exclusion criteria listed in this protocol.

3. Fax or send via e-mail the eligibility checklist (checklist to be created from each version of this protocol and maintained by the KU Clinical Project Director and clinical team) and all pages of the consent form to the appropriate KUMC study project director.

4. The KU Clinical Project Director or designee will a) validate eligibility and b) register the participant on the study, assigning the participant to a treatment group

5. The KU Project Director or designee will send an email confirmation of the registration to the person initiating the registration immediately following the registration.

# 16 ASSESSMENT OF SAFETY

## 16.1 Specification Of Safety Parameters

Analyses will be performed for all participants having received at least one dose of study drug / one administration of therapy.
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 and toxicity assessment. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

Information and links regarding CTCAE version 5.0 can be found at the CTEP website:

*https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50*

A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

*https://view.officeapps.live.com/op/view.aspx?src=https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5.0.xlsx*

The investigators in this study will use this document for assessing and reporting of adverse events.

### 16.1.1 Definition Of Adverse Events (AE)

Text below in italics is verbatim from "Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies", issued December 2012 by U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. The guidance may be retrieved from:

*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf?source=govdelivery*

Text below not italicized and in brackets [ ] , has been added for clarification related to this study by the study funder, TESARO, Incorporated.

**Adverse Event [21 CFR 312.32(a)]**
*An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.*

*An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.*

[AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time after the time of signing informed consent, including baseline or washout periods, even if no study treatment has been administered.]

**Suspected Adverse Reaction [21 CFR 312.32(a)]**

*Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.*

*Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.*

**Unexpected [21 CFR 312.32(a)]**

*An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application… "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the Particular drug under investigation.*

*This definition relies entirely on a listing of the adverse events or suspected adverse reactions in the investigator brochure…as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is unexpected. This means that events not listed for the Particular drug under investigation in the investigator brochure are considered "unexpected" and those listed are considered "expected." When new adverse event information is received, it is the sponsor's responsibility to determine whether the event is "unexpected" for safety reporting purposes.*

**Serious [21 CFR 312.32(a)]**

*An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization* [* ≥ 24 hours] *or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.*

[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.
*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 captured in medical history section in the eCRF. Complications experienced during these hospitalizations must be reported as AEs (or SAEs, if hospitalization is prolonged due to the AE).]

**Life-threatening**
*An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death*

**Per funder, TESARO:**
**Adverse Events of Special Interest (AESIs)**
Selected nonserious AEs and SAEs are also known as Adverse Events of Special Interest.

Any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor-Investigator Institution and TESARO is required.
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

AESIs should be reported on SAE Report Forms whether serious or not, as follows:

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

### 16.1.2 Relationship To Study Agent

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from study drug administration: The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): participant's response after drug discontinuation (de-challenge) or participants response after

study drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.

- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have.
- Concomitant medication or treatment: The other drugs the participant is taking or the treatment the participant receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual participant's pharmacodynamics should be considered.

Attribution is the relationship between an adverse event or serious adverse event and the study treatment.

Attribution will be assigned as follows:

| Relationship<br>(To be provided TO TESARO) | Attribution<br>(To be used when reporting to KU) | Description |
|---|---|---|
| Not related | Unrelated | The AE is clearly **NOT** related to the study treatment. |
| Not related | Unlikely | The AE is **doubtfully related** to the study treatment. |
| Related | Possible | The AE **may be related** to the study treatment |
| Related | Probable | The AE is **likely related** to the study treatment. |
| Related | Definite | The AE is **clearly related** to the study treatment. |

Table from *https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf*

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/or study procedures) 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/or study procedures) 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.

### 16.1.3 Severity Assessment

All AEs will be assessed by the Investigator for severity according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0The CTCAE severity grades 1 through 5 provide unique clinical descriptions of severity of each adverse event.

Information and links regarding CTCAE version 5.0 can be found at the CTEP website:

*https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50*

A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

*https://view.officeapps.live.com/op/view.aspx?src=https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5.0.xlsx*

.
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 above with title DEFINITION OF ADVERSE EVENTS (AE). 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.

## 16.2 Reporting Procedures

### 16.2.1 Adverse Event Reporting

Information for adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported in the study Case Report Form (CRF) as described in the following sections.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, or reported by patient), must be documented.

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 SAEs will be collected from the signing of the ICF and for at least 30days after the last dose of protocol therapy. SAEs considered by the Investigator to be related to study medication will be reported regardless of the timeframe from last dose of protocol therapy.

All AEs will be documented for each patient from the signing of the ICF and for at least 30days after the last dose of protocol therapy.

Concomitant illnesses that existed before entry into the study are to be documented as medical history and will not be considered AEs unless the illness worsens after initiating protocol therapy.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented but not reported as an SAE. 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.

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 you were last asked?" 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.

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom.

Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the Sponsor- investigator.

Study participants should also be instructed to report any new serious post-study event(s) that might reasonably be related to participation in this study.

Medical conditions/diseases, or cancer related symptoms present before starting study treatment are considered adverse events only if they worsen after initiation of study drug.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or require therapy. In this case they will be recorded on the Adverse Events CRF, along with the associated signs, symptoms or diagnosis.

### 16.2.2 Recording Adverse Events And Documentation In *CRIS*

All **expected** and **unexpected** adverse events and serious adverse events occurring after the participant has signed the informed consent until 30 days after last dose of study drug must be fully recorded in the participant's case record form.

All AEs and AESIs and SAEs regardless of causality must be entered in the KU implementation of Velos eResearch; at KU, called the Comprehensive Research Information System (CRIS). Unexpected and expected adverse events must be entered within 5 days and include: new unexpected adverse events; worsening baseline conditions; clinically significant laboratory findings; disease-related signs and symptoms that were not present at baseline, and any event of findings that the Investigator feels is clinically significant.

Documentation must be supported by an entry in the participant's file. A laboratory test abnormality considered clinically significant (e.g., causing the participant to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event). Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

### 16.2.3 Serious Adverse Event Reporting

For serious adverse events, the clinical research site will follow local IRB policies and procedures

All AESIs and SAEs regardless of causality must be entered into CRIS within 24 hours. Entering the event into CRIS will send an automatic email to the study Investigator, study Clinical Project Director, study Regulatory team and the KUCC DSMC.

Follow-up source documentation is required within 5 days.

Send all supporting documents to:

KUCC DSMC
Fax: 913-588-4701
Email: *kucc-dsmc@kumc.edu*

**AND**

### 16.2.4 Reporting To Funder, TESARO

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

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

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

Per regulatory requirements, if an event is assessed by the Sponsor-Investigator as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor-Investigator to submit the SUSAR to Regulatory Authorities according to applicable regulations.

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) per the governing institutional requirements and in compliance with local laws and guidelines.

| TESARO AE and Pregnancy Reporting Information |
|---|
| *dsa.aetesaro@ashfieldpv.com*<br>Fax Number: +1-866-433-3038 |

On at least an annual basis, the Sponsor-Investigator will provide a copy of the safety reports submitted to applicable Regulatory Authorities or IECs. Annual reports should be provided to TESARO within 3 business days of submission to the applicable regulatory body.

**NOTE:** On a quarterly basis the Sponsor-Investigator will provide TESARO with a line listing of all adverse events (serious and non-serious) received during a defined quarter. The line listing will include a participant ID, the AE term, onset date, outcome, causality assessment, severity, and study drug dosing information.

The Investigator must **report** all pregnancies and the outcomes to the Sponsor-Investigator and to TESARO. The Sponsor-Investigator has the responsibility to monitor the outcome of all pregnancies reported during the clinical study.

The funder, TESARO has confirmed that each pregnancy must be **reported** by the Investigator to the Sponsor-Investigator and to TESARO 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 (to TESARO) unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. The pregnancy must be reported to the Sponsor-Investigator and to TESARO on a Pregnancy Outcome Report Form within 24 hours of becoming aware - even if the patient has withdrawn from the study or the study has finished. The pregnant participant, or pregnant partner, will be asked to consent to allowing the investigator to follow the pregnancy, and document the course and the outcome.
**If the pregnant partner (or pregnant participant) consent to allowing the investigator to follow the pregnancy course and outcome, follow these procedures:**

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-Investigator Institution and TESARO within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

**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, the Investigator and the funder should be notified immediately, and the patient should be observed closely for AEs. 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 documented. An overdose (including an AE or SAE resulting from the overdose, if any) will be reported as an SAE.
- **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 TESARO product must be reported on a Special Situations Report Form to the Sponsor-Investigator Institution and to TESARO within 5 business days of awareness regardless of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an AE, an SAE Report Form must also be submitted to the Sponsor-Investigator Institution and to TESARO within 24 hours of awareness.

### 16.2.5 Reporting Product Quality Complaints for Niraparib to Funder, TESARO

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 TESARO Call Center:

**(US Call center**: *Tesaro@medinfodept.com* , 1 working day of first becoming aware of the possible defect.

This report to TESARO may also be made by telephone to the designated TESARO representative at: (**1-844-4TESARO**) or by fax to the Call Center (**US Call Center: 1-913-451-6409)**.

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 AESI/SAE, the AESI/SAE must be reported separately in accordance with the protocol, and the AESI/SAE report should mention the product quality complaint.

### 16.2.6 Summary Of Expedited Serious Adverse Event Reporting

AND Per funder, TESARO:
Please note that causality should be assessed as **related or not related** when provided to TESARO

| | **Relationship to Study Drug** | **IRB** | **CRIS (KU DSMC and PI)** | **TESARO** |
|---|---|---|---|---|
| Unexpected SAE/AESI | Related | Per local IRB reporting policy | 24 hrs | 24 hrs |
| Unexpected SAE/AESI | Not-related | Per local IRB reporting policy | 24 hrs | 24 hrs |
| Expected SAE/AESI | Related | Per local IRB reporting policy | 24 hrs | 24 hrs |
| Expected SAE/AESI | Not-related | Per local IRB reporting policy | 24 hrs | 24 hrs |

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/or study procedures) 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/or study procedures) 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.

### 16.2.7 Reporting Of Pregnancy at KU

Any pregnancy occurring on study must be recorded as an adverse event in CRIS.

# 17 DATA AND SAFETY MONITORING

## 17.1 DSMC Oversight And Monitoring Plan

The multidisciplinary KUCC Data and Safety Monitoring Committee (DSMC) is charged with overseeing the monitoring of participant safety, conduct and scientific progress of research protocols, and the validity and integrity of the data for clinical trials. The KUCC DSMC has the authority to require amendments, suspend, or terminate any research activities that fall within its jurisdiction, and can institute other appropriate actions as needed to protect participant safety.

The study will be monitored at appropriate intervals, no less than those assigned by the KUCC Protocol Review and Monitoring Committee, to assure compliance to GCP and to assess the data quality and study integrity. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data

## 17.2 Safety Review And Oversight Requirements

### 17.2.1 Serious Adverse Event

Serious adverse events that require expedited reporting will be reviewed by the DSMC Chair or designee who will determine if immediate action is required. If determined to be necessary by the DSMC, all participating sites will be notified of the event and any resulting action within one working day of this determination.

### 17.2.2 Review Of Adverse Event Rates

Once per month, adverse event rates will be monitored by the DSMC Coordinator. If any study site has had 2 or more of the same SAE/AESI reported within one month, or more than 6 of the same SAE/AESI in 6 months, the DSMC will review summaries of SAE/AESIs, and discuss events in detail with the PI. The DSMC chair or designee determines whether further action is required. The DSMC Coordinator ensures that collaborating investigators and IRBs for all Participating sites are notified of any resulting action.

### 17.2.3 Study Safety And Progress

An overall assessment of toxicities as described in the protocol is reviewed at DSMC meetings. This review enables DSMC committee members to assess whether significant risks are occurring that would warrant study suspension/closure or protocol amendment.

The DSMC is an autonomous committee. However, its actions are communicated to other committees engaged in oversight of clinical research at KUCC. The PI is responsible for forwarding all DSMC letters,

including those recommending continuation of the study, to the IRB and PRMC. DSMC recommendations for modifications to the trial are forwarded to the Deputy Director of KUCC. The PI is notified of this recommendation, and is expected to alert all collaborating investigators about the DSMC action. At this time the PI may appeal the Committee's decision to the Deputy Director of KUCC or their designee. The Deputy Director of the KUCC or their designee will notify the PI if he/she concurs with the DSMC's recommendation, including suspension or closure.

### 17.3 Unblinding Rules

None

## 18 REGULATORY CONSIDERATIONS

### 18.1 Protocol Review And Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Sponsor-Investigator will disseminate protocol amendment information to all study team members.
All decisions of the IRB concerning the conduct of the study must be made in writing.

## 19 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

### 19.1 Ethical Standard

**Ethics and Good Clinical Practice (GCP)**
This study is to be conducted according to the following considerations, which represent good and sound research practice:

1. State laws

2. ICH Consolidated Good Clinical Practice: Guidelines (E6)
   *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf*

3. US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

4. *http://www.ecfr.gov/cgi-bin/ECFR?page=browse*

With attention to the following specific regulations:

*a.* Title 21 Part 50 – Protection of Human Subjects
*b.* Title 21 Part 56 – Institutional Review Boards
*c.* Title 21 Part 312 – Investigational New Drug Application Responsibilities of Sponsors and Investigators

*5.* Institutional research policies and procedures:

*http://policy.ku.edu/research/human-subjects*

*AND*

*http://www.kumc.edu/human-research-protection-program/institutional-review-board/policies-and-regulations.html*

### 19.2 Informed Consent Process

**Informed Consent**
All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

## 20 DATA HANDLING AND RECORD KEEPING

### 20.1 Data Collection And Management Responsibilities

Case report forms (CRFs) will be completed for each participant enrolled. All CRFs will be customized per this study, in order to emphasize completeness and accuracy. The medical chart and any other clinical worksheets, procedural reports, etc. will be the source documentation of data captured into the study database.

### 20.2 Study Records Retention

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records and clinic charts, laboratory and pharmacy records, signed ICFs, participant diaries and pathology reports. All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

## 20.3 Protocol Deviations

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB and DSMC according to the local reporting policy.

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# 22 APPENDICES

## Appendix A: ECOG Performance Status

### ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

| GRADE | ECOG PERFORMANCE STATUS |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any selfcare; totally confined to bed or chair |
| 5 | Dead |

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.

## Appendix B: KU ELECTRONIC SAE/AESI Form

The KU SAE/AESI form is electronic using an adverse event module in the CRIS platform.

**The KU SAE/AESI form, from electronic CRIS platform.**

Study Number: View Title

**Adverse Event Type** * Select an Option

Category Select

from Dictionary Calculate

Adverse Event Name

Toxicity

Toxicity Desc

Severity/Grade

Severity/Grade Desc

MedDRA code

Dictionary

Other Description

Treatment Course

**Start Date** *

Stop Date

AE Discovery Date

AE Logged Date

**Entered By** * Angelica Allen Select User

Reported By Select User

**Attribution** Select an Option

Linked To Select Adverse Events

Outcome Information

Outcome Type

- ☐ Death Date
- ☐ Life-threatening
- ☐ Hospitalization
- ☐ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention
- ☐ Recovered

**The KU SAE/AESI form, from electronic CRIS platform.**
(Continued from previous page)

| | |
|---|---|
| Action | Select an Option |
| Recovery Description | Select an Option |
| Outcome Notes | |

**The KU SAE/AESI form, from electronic CRIS platform.**
(Continued from previous page)

Additional Information

- ☐ Form Completed
- ☐ Listed in consent form
- ☐ Unexpected
- ☐ Listed in protocol
- ☐ Protocol violation
- ☐ Patient dropped out due to this event
- ☐ Dose Limiting Toxicity
- ☐ Local monitoring report
- ☐ Interim findings and safety monitoring report
- ☐ Publication
- ☐ Change in FDA labeling
- ☐ Death
- ☐ Unanticipated adverse device event
- ☐ Serious and unexpected
- ☐ Possibly or probably related
- ☐ Other
- ☐ Form Submitted to Sponsor, If applicable
- ☐ Serious
- ☐ Form Submitted to IRB / HSC

**The Following were Notified:**

| | | |
|---|---|---|
| ☐ IRB | Date | |
| ☐ FDA | Date | |
| ☐ Sponsor | Date | |
| ☐ Others | Date | |

Notes

Form Status: Select an Option  e-Signature *  Submit

Important Links

## KU CRIS electronic SAE/AESI Form Guidance/Information

*If more detailed instructions are needed, see the CRIS User's Guide found in the Guidance Documents library on the CTO SharePoint site (https://share.kumc.edu/RIC/cancercenter/CTMSR_SOPs/SitePages/Home.aspx)*

**All are required fields when entering an adverse event unless indicated:**

1. **Adverse Event Type:** Baseline, Adverse Event, Serious Adverse Event or Late Adverse Event as defined by protocol.
2. Always 'Select from Dictionary' to complete the **Adverse Event Name** and **Grade**. This will automatically fill the **Category** through **Dictionary** fields on the form.
3. **Other Description (optional):** This is for any details and additional information about the event.
4. **Treatment Course (optional):** Enter the cycle of therapy the patient was receiving when the event started
5. **Start date:** The first date the event occurred.
6. **Stop date (if applicable):** The last date the event occurred.
7. **AE Discovery Date and AE Logged Date**
   a. AE Discovery Date is the date the event was reported to the study personnel
   b. AE Logged Date is the date the event was entered into CRIS
8. **Entered By:** This is the person entering the data into CRIS.
9. **Reported By (optional):** This is the person that documented the event in the source documents
10. **Attribution:** Select 'Attribution by drug entered below'. See Adverse Event – More Details at bottom of form.
11. **Linked To (optional):** A previously entered AE may be selected if it is directly related to the AE being entered.
12. **Outcome Type (Required field for Serious Adverse Events only):** Select all criteria that fit the reported event. Do not use *Required Intervention* or *Recovered*. These are options elsewhere on the form.
13. **Action:** Select most appropriate action related to the adverse event.
14. **Recovery Description:** Select most appropriate and update as patient status changes or until recovered.
15. **Outcome Notes (optional):** Comment area for any additional details regarding the action or recovery of the adverse event.
16. **Additional Information (optional)**
    a. Dose Limiting Toxicity – Mark if this is a phase I study and event is DLT as defined by protocol.
17. **The Following were Notified (if applicable, entered by regulatory coordinator):** Provide the dates the final report was mailed or faxed to the listed organizations.
18. **Notes (optional):** Provide any other detail regarding the submission of reports.
19. **Adverse Event – More Details**
    a. **Date last study drug dose given**: Required for serious adverse events. Enter last date any study treatment was given prior to event.
    b. **Expectedness**: Select the expectedness of the adverse event in relation to the study as determined by the treating investigator.
    c. **Drug**: Enter the primary drug name as defined in the protocol. If more than one drug and the protocol is an IIT, drug 1, 2, 3, etc. should be defined in CRF guidance.
    d. **Attribution**: Select attribution (relationship) to the drug as determined by the treating investigator.
    e. **Action**: Select most appropriate action for each drug in relation to the adverse event.

05/01/2017 – Version 7 Questions: Michele Park – 913-588-4791

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