A Phase II Trial of the PARP Inhibitor, Niraparib, in BAP1 and other DNA Damage Response (DDR) Pathway Deficient Neoplasms

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ABBREVIATIONS

αKG	α-ketoglutarate
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase (also SGPT)
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase (also SGOT)
AUC	Area Under Curve
BER	Base-Excision Repair
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CE	Carboxylesterases
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
COSMIC	Catalogue of Somatic Mutations in Cancer
CR	Complete Remission
CRF	Case Report Form
CRO	Clinical Research Office
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trials Management System
DDR	DNA Damage Response
DISC	Data Integrity and Safety Committee
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DSB	Double-Strand Break
DUB	Deubiquitinating
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FDG	Fluorodeoxyglucose Positron Emission
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GSK	Glaxo Smith Kline
HDPE	High-Density Polyethylene
HR	Homologous Recombination

HRD	Homologous Recombination Deficiency
HRT	Hormone Replacement Therapy
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDH	Isocitrate Dehydrogenase
IHC	Immunohistochemistry
IR	Ionizing Radiation
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram(s)
LDH	Lactic Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NGS	New Generation Sequencing
NSAE	Non-Serious Adverse Event
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly ADP-Ribose Polymerases
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PMO	Project Management Office
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial Remission
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
SAE	Serious Adverse Event

SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase (also AST)
SGPT	Serum Glutamic Pyruvate Transaminase (also ALT)
SSB	Single Strand Break
SUSAR	Suspected Unexpected Serious Adverse Event
T_{max}	Time to Maximum Plasma Concentration
TEAE	Treatment Emergent Adverse Event
TMZ	Temozolomide
UF	University of Florida
UFHCC	University of Florida Health Cancer Center
UGT	University of Florida Health Cancer Center
ULN	UDP-Glucuronosyltransferases
US	Upper Limit of Normal
VUS	United States
WBC	Variants of Unknown Significance
WHO	White Blood Cell
WOCBP	World Health Organization

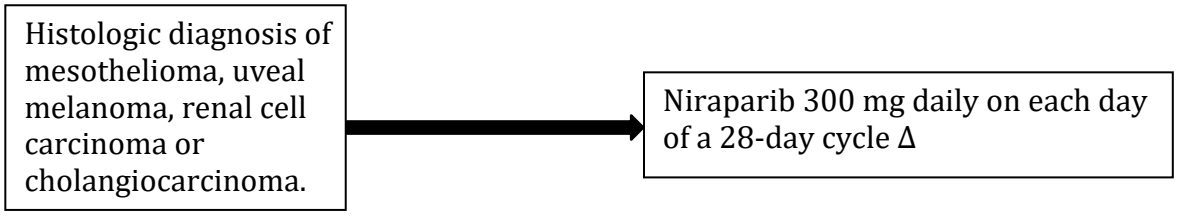
Site Protocol Signature Page

A Phase II Trial of the PARP Inhibitor, Niraparib, in BAP1 and other DNA Damage Response (DDR) Pathway Deficient Neoplasms

Study Principal Investigator:	_____ Signature of Investigator	_____ Date
	_____ Printed Name of Investigator	
	_____ Name of Facility	
	_____ Location of Facility (City/State)	
Local Principal Investigator:	_____ Signature of Investigator	_____ Date
	_____ Printed Name of Investigator	
	_____ Name of Facility	
	_____ Location of Facility (City/State)	
	By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.	

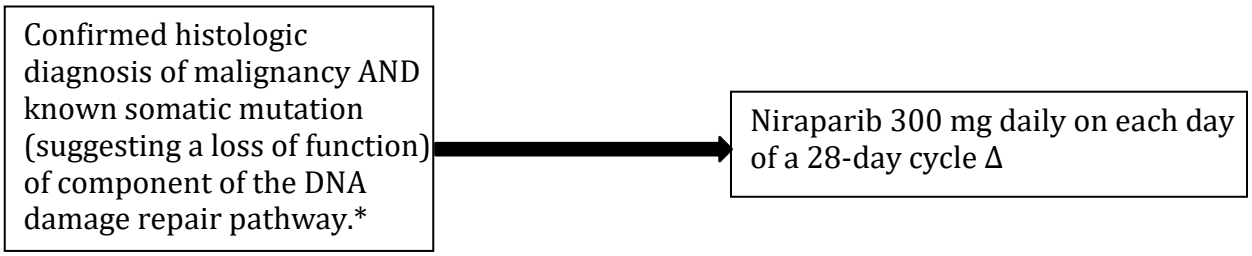
STUDY SCHEMA

Cohort A (n=35)



Disease status assessed every 8 weeks and continued until progression or unacceptable toxicity

Cohort B (n=12)



Δ If subjects baseline body weight is < 77kg (170 pounds) or baseline platelet count is < 150,000/µl starting dose of 200 mg daily will be administered

*ARID1A, ATM, ATR, BACH1 (BRIP1), BAP1, BARD1, BLM, CHEK1, CHEK2, CDK2, CDK4, ERCC, FAM175A, FEN1, IDH1, IDH2, MRE11A, NBN (NBS1), PALB2, POLD1, PRKDC (DNA-PK), PTEN, RAD50, RAD51, RAD52, RAD54, RPA1, SLX4, WRN, or XRCC

Accrual Goal: 47 total subjects

PROTOCOL SYNOPSIS

Title:	A Phase II Trial of the PARP Inhibitor, Niraparib, in BAP1 and other DNA Damage Response (DDR) Pathway Deficient Neoplasms
Funding Organization:	TESARO/GSK
Investigational Agent Supplier:	TESARO/GSK
Rationale:	BAP1 is an ubiquitin ligase that is critical in helping to regulate the cell cycle, cellular differentiation, cell death, and DNA damage response. This protein also acts as a tumor suppressor as highlighted with the hereditary cancer syndrome associated with germline mutations in the gene harboring BAP1. Most relevant to our study is BAP1s association with DNA damage response/repair. As BAP1s (BRCA1 Associated Protein 1) name implies it is intimately involved with double stranded DNA break repair. This protocol aims to exploit the concept of synthetic lethality with the use of niraparib, an inhibitory of Poly-ADP Ribose Polymerase (PARP). Along these lines, this protocol is going to include tumors known to harbor BAP1 mutations (cohort A) as well as tumors with alterations in the DNA damage response (DDR) pathway (cohort B). The subjects of interest would have exhausted all standard lines of therapy and therefore this study would fill a significant medical need.
Objectives:	Primary: • To determine the objective response rate (ORR) for subjects with BAP1 and other DDR repair pathway deficiencies treated with niraparib. Secondary: • To determine the median progression free survival (PFS) and estimate PFS at 3 and 6 months in each cohort and histologic subsets of subjects.To estimate the median overall survival (OS) • To determine the incidence, severity, and reversibility of toxicities in subjects treated with niraparib. Exploratory: • To explore the impact that specific DNA repair mechanism deficiencies have on tumor PARP inhibition • To explore alternate biomarkers that predict response to PARP inhibition

Study Design:	This is a prospective, open-label phase II study in two biologically distinct cohorts.
Accrual Goal:	A total of 47 subjects (Cohorts A and B). Cohort A: 35 subjects in histologies that enrich for BAP1 mutations Cohort B: 12 subjects with any histology containing a pre-specified DNA DDR repair mutation Optional Cohort A expansion within each specific histology
Inclusion Criteria:	Individuals eligible for study participation must meet the following criteria: A. Must be ≥ 18 years of age B. A clinical diagnosis of incurable cancer confirmed histologically. C. (For Cohort A) Must have confirmed diagnosis consistent with uveal melanoma, mesothelioma, renal cell carcinoma (clear cell subtype), or cholangiocarcinoma. D. (For Cohort B) Must have a pre-specified DNA DDR repair mutation including any one of the following: ARID1A, ATM, ATR, BACH1 (BRIP1), BAP1, BARD1, BLM, CHEK1, CHEK2, CDK2, CDK4, ERCC, FAM175A, FEN1, IDH1, IDH2, MRE11A, NBN (NBS1), PALB2, POLD1, PRKDC (DNA-PK) PTEN, RAD50, RAD51, RAD52, RAD54, RPA1, SLX4, WRN, or XRCC. Only CLIA certified next generation sequencing (NGS) assays are acceptable. Variants of unknown significance (VUS) will be allowed to enroll on study. Cohort B enrollment is histology agnostic. E. Must have formalin-fixed paraffin embedded (FFPE) tissue available for research purposes. Tissue must have been obtained within the last 3 years from a core or excisional biopsy. F. Measurable disease by RECIST (v 1.1) criteria (prior radiation therapy to any indicator lesion must have demonstrated progressive growth of the lesion to be considered measurable). G. Adequate organ function as defined as: • Absolute neutrophil count (ANC) ≥ 1,500/µL • Hemoglobin ≥ 9g/dL • Platelets ≥ 100,000/µL • Total bilirubin ≤ 1.5 ULN or direct bilirubin ≤ 1 x ULN • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN; if liver metastases present, then AST and ALT must be ≤ 5 x ULN • Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min using Cockcroft-Gault equation H. A medical history with prior exposure to standard systemic therapy (having exhausted or declined all known and currently

	approved effective life prolonging therapies). I. An ECOG Performance Status less than or equal to 1. J. A life expectancy of greater than or equal to 12 weeks. K. Written informed consent obtained from the subject and the ability for the subject to comply with all the study-related procedures. L. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 7 days prior to the first dose AND be using an adequate method of contraception to avoid pregnancy throughout the study and for at least 180 days after the last dose of study drug to minimize the risk of pregnancy. An adequate method of contraception is defined as contraceptive methods with a failure rate of less than 1% per year when used consistently and correctly. Subjects and their sexual partners who have undergone a vasectomy or tubal occlusion must also use a male condom with spermicide. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as: Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or for women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL. M. Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (e.g., abstinence, condoms, vasectomy) throughout the study and should avoid conceiving children for 180 days following the last dose of study drug. In addition, men must not donate sperm during niraparib therapy and for 180 days after receiving the last dose of niraparib. N. Subjects must agree to not donate blood during the study or for 90 days after the last dose of study treatment. O. Subjects receiving oral corticosteroids may continue as long as their dose is stable for least 4 weeks prior to initiating protocol

	therapy. P. If a new biopsy is needed for diagnostic reasons, the biopsy must be performed from a tumor site that is not the only site of measurable disease.
Exclusion Criteria:	Subjects with any of the following will not be eligible for study participation: A. A medical history of prior exposure to PARP inhibitors (olaparib, niraparib, rucaparib, etc.). B. Subject has received or is planning to receive live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. C. A medical history demonstrating a BRCA1 or BRCA2 mutation. D. A pathologic diagnosis of prostate cancer as the cancer to be treated in cohort B. E. Subject is simultaneously enrolled in any other interventional clinical trial. F. Subject has had major surgery ≤ 3 weeks of enrollment, and subject must have recovered from any effects of any major surgery. G. Subject has 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. H. Subject has had radiotherapy encompassing > 20% of the bone marrow within 4 weeks of the first dose. I. Subject has a known hypersensitivity to the components of niraparib or the excipients. J. Subject received a transfusion (platelets or red blood cells) ≤ 4 weeks of the first dose of study treatment. K. Subject has received colony stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte macrophage colony stimulating factor, or recombinant erythropoietin) within 4 weeks prior to initiating protocol therapy. L. Subject has more than one active malignancy at the time of enrollment (Subjects with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen [as determined by the treatment physician and approved by the PI] may be included). M. Subject has known, active symptomatic brain or leptomeningeal metastases.

	N. Subject has had any known Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment. O. Subject has any known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). P. Females or males of childbearing potential who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for at least 180 days after the last dose of study drug. Q. Females who are pregnant or breastfeeding. R. History of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician or study PI. S. Prisoners or subjects who are involuntarily incarcerated. T. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness. U. Subjects demonstrating an inability to comply with the study and/or follow-up procedures.
Efficacy Assessments:	RECIST (version 1.1) and laboratory evaluations
Statistical Considerations:	The sample size of 35 patients from Cohort A is based on a Simon optimal two stage design (one-sided alpha 0.05; Beta 0.10) to increase the response rate from baseline <10% (H0) to 30% (H1) in this histologically selected patient population. The second stage of the study will proceed to 35 total patients if 3 or more patients from the first 18 enrolled have an objective response. If 7 or more patients respond among the 35, Cohort A treatment will be considered a success. The sample size of 12 patients from Cohort B is based on an increase in the response rate from baseline <10% (H0) to 50% (H1) in this molecularly selected/enriched patient population (one-sided alpha 0.05; Beta 0.10). If 5 or more patients respond among the 12, Cohort B treatment will be considered a success. Cohort A and B success will be assessed independent of one another. Thus, a total sample size of 47 patients is proposed. Optional Cohort Expansion: In Cohort A only, independent of the final RR for the entire cohort, if the ORR is >30% (H1) within any one of the

	histology categories required for eligibility (i.e., mesothelioma alone), an expansion cohort of an additional 20 patients (to obtain 18 evaluable) of that specific histology will be considered. This can be performed for each of the four histologies defined in Cohort A. This provides 80% power to determine this degree of activity.
Estimated Enrollment Period:	30 months
Estimated Study Duration:	Enrolled study participants will continue on study for approximately8 weeks, unless otherwise clinically indicated, before tumor status is assessed radiographically. Total study duration is dependent on imaging studies (i.e. stable disease, progression, or response) and/or subject tolerability of study drug.

1. BACKGROUND & RATIONALE

BAP1s Role in DNA Repair

The post-translational modification of DNA repair proteins is essential for their function. This includes the addition or removal of ubiquitin. The covalent binding of ubiquitin to proteins can serve as a targeting signal, can modify protein activity, or affect its half-life1. Protein ubiquitination is linked to DNA damage signaling, DNA damage repair, and transcriptional silencing2-14. BRCA1 is an ubiquitin ligase, and it ubiquitinates itself and other target proteins. This activity is balanced by deubiquitinating (DUB) enzymes, which also interact with a variety of proteins during the repair of double-stranded breaks (DSB). One of these DUBs is BAP1 (BRCA1 Associated Protein 1), which binds to the zinc finger moiety of BRCA1. First described in 1998, BAP1 is a 729 amino acid nuclear-localized protein that contains ubiquitin carboxy-terminal hydrolase activity15. BAP 1 also functions as a subunit of a multi-protein complex associated with regulating the cell cycle, cellular differentiation, cell death, and DNA damage responses12,16,17. BAP1 also increases the activity of BRCA1 3-fold to 4-fold, though it does not appear to directly modify BRCA1 itself16.

Several lines of evidence also point to BAP1 as a tumor suppressor. The gene is located on chromosome 3p21.1. This is a region that is nearly universally deleted in small cell lung cancer, the vast majority of non-small cell lung cancers, as well as in some breast and renal cell carcinomas, among other malignancies18. Accompanying this loss of heterozygosity are a variety of inactivating mutations; affecting either one of the two nuclear localizing regions of the BAP1 protein DUB catalytic site, or in some cases, epigenetic silencing of the BAP1 gene.

Germline mutations in BAP1 are associated with an autosomal-dominant hereditary cancer syndrome which is associated with an increased risk of developing uveal melanoma, mesothelioma, cutaneous melanocytic lesions, atypical Spitz tumors, and clear cell renal carcinomas. There also appears to be a less defined increased risk of meningiomas, lung adenocarcinomas, and neuroendocrine carcinomas.

PARP inhibition and BAP1 Deficiency

Poly (ADP-ribose) polymerases (PARP-1 and -2) are nuclear proteins that contain three functional domains19, the most relevant to our study is the two zinc fingers which are important for the binding of PARP1 to single-stranded and double-stranded DNA breaks20. When a single- strand DNA break occurs PARP binds to the end of the broken DNA strand. Once activated, PARP catalyzes the addition of long polymers of ADP-ribose on several proteins associated with chromatin, including histones and various DNA repair proteins (including PARP). This results in chromatin relaxation, recruitment of DNA repair proteins and repair of DNA breaks. PARP is crucial in sensing DNA damage and signaling base-excision-repair (BER) and single strand break

(SSB) repair pathways. Unrepaired SSBs, by way of PARP inhibition, move through DNA replication (S phase) and when a replication fork is reached the SSB will become a DSB21.

A classic example of the importance of PARP activity in DNA DSB repair is breast cancer gene (BRCA)-1 and BRCA2- deficient cells. BRCA is critical for HR in cells and these cells become "addicted" to other pathways of DNA repair (i.e. PARP and BER) to allow for continued replication and survival. This concept of loss or inhibition of a gene, and its product, that the cell relies on to compensate for another gene loss causing the cell's subsequent demise is referred to as synthetic lethality21,22. It has been proven in the lab that cells that are deficient in HR (i.e. BRCA deficient) are hypersensitive to PARP inhibition23,24. There is also good evidence of the clinical efficacy of PARP inhibition in the setting of subjects with BRCA mutations. The PARP inhibitor olaparib was approved by the Food and Drug Administration (FDA) in December of 2014 for treatment of refractory (≥ 3 lines of therapy) ovarian cancer which harbors a BRCA 1/2 mutation. In this select population results showed an objective response rate of 34% and duration of response of 7.9 months. Another PARP inhibitor, rucaparib, was recently approved for the same indication. Additionally, the PARP inhibitor, niraparib, was approved by the FDA in March of 2017 for the maintenance treatment of the adult population with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in individuals who are in complete or partial response to platinum-based chemotherapy.

Lab work at the University of Florida (Hromas, personal communication and data on file) was done to determine if synthetic lethality applies to BAP1 mutant cancers. Olaparib was given to BAP1-mutant mesothelioma, H-Meso 001A, cells in clonogenic assays. Olaparib demonstrated significant cytotoxic activity with nearly 90% cell kill. The same cell line, but with loss of function mutations in ATM, Ligase III or ERCC4 (all components of the DNA DSB repair pathway) were treated with olaparib and synthetic lethality (70-90% cell kill) was again exhibited. Taken together, it is postulated that PARP inhibition with niraparib will result in significant cytoreduction in tumors that lack functional BAP1, as well as other deficiencies of the DNA damage repair pathway.

1.1 Study Rationale

This protocol will evaluate the PARP inhibitor, niraparib, in a phase II open label study that aims to exploit the concept of synthetic lethality in subjects with tumors known to potentially harbor BAP1 mutations (cohort A) and tumors with a known somatic gene mutation involved in DNA damage pathway repair (cohort B).

1.1.1 Rationale to Study Uveal Melanoma, Mesothelioma, Renal Cell Carcinoma, and Cholangiocarcinoma in Cohort A

Functionally, BAP1 appears to be required for cell genomic stability and survival following DNA damage. Several lines of pre-clinical evidence conducted by University of Florida investigators (Hromas, personal communication and data on file) support this line of scientific pursuit. BAP1 activation through phosphorylation on serine 592 is enhanced by cellular exposure to ionizing radiation (IR) in U2OS and HEK293 cell lines. This BAP1 phosphorylation is significantly diminished or completely absent after the addition of caffeine which inhibits ATM/ATR kinases. A number of DNA damaging agents; including etoposide, cisplatin, and hydroxyurea also induce BAP1 phosphorylation. To confirm that BAP1 regulates the stability of key homologous recombination (HR) components, studies have demonstrated that two distinct BAP1 siRNAs resulted in instability of RNF168, an E3 ubiquitin-protein ligase required for accumulation of DNA repair proteins, with and without IR. The RNF168 protein level instability in BAP1 depleted cells is reversed by a proteasome inhibitor (MG132) again with and without IR. After depletion of BAP1 in the dual reporter cell line, HR was significantly impaired with identification of BAP1 co-localizing with the p53 binding protein in ionizing irradiation-induced foci, which mark DNA DSBs. Thus, BAP1 appears required for proper DNA DSB repair in the HR pathway.

Somatic mutations of BAP1 resulting in loss of expression or function have been reported in up to 47% of uveal melanomas, 23% of mesotheliomas, 15% of clear cell renal cell carcinomas, and in 26% of intrahepatic cholangiocarcinomas25-28. Inclusion of these histologies in Cohort A will enrich for tumors with BAP1 deficiencies and support the testing of this clinical hypothesis. Thus, cohort A serves as a means to determine whether BAP1 mutations confirm PARP activity regardless of histology. BAP1 status will be determined post-hoc for verification, but will use the histology defined here as a surrogate to enrich for this biomarker.

1.1.2 Rationale to Study Other DNA Repair Pathway Deficiencies in Cohort B

We have strategically chosen a number of DNA pathway repair genes and their respective gene products to investigate prospectively in cohort B. The rationale is the same as with BAP1 in terms of inducing synthetic lethality with the combination of PARP inhibition. These genes of interest include ARID1A, ATM, ATR, BACH1 (BRIP1), BAP1, BARD1, BLM, CHEK1, CHEK2, CDK2, CDK4, ERCC, FAM175A, FEN1, IDH1, IDH2, MRE11A, NBN (NBS1), PALB2, POLD1, PRKDC (DNA-PK), PTEN, RAD50, RAD51, RAD52, RAD54, RPA1, SLX4, WRN, or XRCC. Each of these genes is responsible for a component of the DNA damage repair process (see section 1.2.3). Thus, a mutation resulting in loss of function of one of these genes could also provide susceptibility to PARP inhibition similar to the way proposed for BAP1 (i.e., synthetic lethality). However, these genetic abnormalities are infrequent in the cancer patient population. This protocol will also retrospectively assess tumors in cohort A for non-BAP1 deficiencies in DNA damage repair. Cohort B enrollment is histology agnostic.

There is also recent evidence that isocitrate dehydrogenase (IDH) 1/2 mutations account for defects in HR29. The normal conversion of isocitrate to α-ketoglutarate (αKG) is mediated by IDH. With IDH mutations, αKG is aberrantly converted to the oncometabolite 2- hydroxyglutarate (which exists in two enantiomers). This oncometabolite was found to directly inhibit α-ketoglutarate-dependent dioxygenases, which in turn caused HR suppression. The investigators were also able to show that IDH1 dependent HR deficiency conferred synthetic lethality with PARP inhibition. Given these findings, we are also including IDH 1/2 mutations for cohort B eligibility to assess this proof of principle.

Given the infrequent mutations and heterogenous histologic tumor types proposed in Cohort B, we are planning descriptive assessments of any response as a proof of principle to justify further testing in later studies.

1.1.3 Details Regarding Additional Genes of Interest

ARID1A (AT-rich Interactive Domain 1A)
Encodes a protein that is a member of the SWI/SNF chromatin-remodeling complex. ARID1A is recruited to DNA DSB via its interaction with ATR. It facilitates processing of DSB to single-strand ends. There is evidence that mutations in this gene can sensitize tumors to PARP inhibition30.

ATM (Ataxia Telangiectasia Mutated)
Encodes a kinase that is a member of the PI3-kinase family. ATM is critical in the early response to DNA damage (particularly DSBs)31. Activated ATM phosphorylates numerous other proteins (i.e. ATR, Chek1, Chek2) in response to DNA damage32.

ATR (Ataxia Telangectasia and Rad3-related)
Encodes a kinase that is a member of the PI3-kinase family. ATR is critical in the early response to DNA damage (as is ATM). ATR primary function is replication fork stability33. ATR is also important in regards to regulating cell cycle by interacting with Chek1, Chek2, and ATM 32.

BACH1 (BRCA1 Associated C-terminal Helicase)
Also known as BRIP1, appears to be the gene product of the Fanconi Anemia gene, FANCJ. The helicase interacts with BRCA1 to assist in DNA DSB repair via HR 34.

BAP1 (BRCA1 Associated Protein-1) See section 1.1

BARD1 (BRCA1 Associated RING Domain 1)
Encodes a protein that forms a heterodimer with BRCA1 and assists in early response to DNA damage. There is preclinical evidence of PARP inhibition suppressing this association and impairing DNA repair.35

BLM (Bloom Syndrome RecQ Like Helicase)
Encodes a helicase involved in DSB repair and HR. More specifically the protein assists in the repair and elimination of stalled replication forks during HR via an interaction with RAD5136.

CHEK1 (Checkpoint Kinase 1)
Encodes a kinase (called Chk1) that forms a complex with ATR and its function is critical with the DDR and cell cycle checkpoint response. The complex is activated in response to single-stranded DNA damage37.

CHEK2 (Checkpoint Kinase 2)
This gene encodes a kinase (called (Chk2) that forms a complex with ATM and helps coordinate DNA DSB repair. Chk2 also interacts and phosphorylates BRCA138.

CDK2 (Cyclin-Dependent Kinase 2)
Encodes a kinase that is essential for regulating cell cycle progression, specifically G1 to S. In response to DNA damage, CDK2 phosphorylates BRCA2 for DSB repair by homologous recombination39.
CDK4 (Cyclin-Dependent Kinase 4)
Encodes a kinase that is essential for regulating cell cycle progression, specifically G1 to S phase. It acts in conjunction with CDK6 and cyclin D family and commits the cell to DNA synthesis.

ERCC (Excision Repair Cross-Complementation) Encodes a helicase involved in nucleotide excision DNA repair32.

FAM175A (also known as Abraxas)
Encodes protein involved in DSB repair by acting as a scaffolding protein to facilitate BRCA1 binding40.

FEN1 (Flap Endonuclease 1)
Encodes a protein involved in single-stranded base excision DNA repair32.

IDH1 (Isocitrate Dehydrogenase 1) See Section 1.2.2
IDH2 (Isocitrate Dehydrogenase 2) See section 1.2.2

MRE11A
Encodes a protein that interacts with ATM and is involved detection and repair of DNA DSB via a complex with RAD50 and NBS1 (MRN). There is in vivo evidence of synthetic lethality with PARP inhibition in endometrial cancer cell lines41.

NBN (NBS1)
Encodes a protein called nibrin that helps form MRN complex. Through interaction with ATM this complex helps with detection and repair of DNA DSB42.

PALB2 (Partner and Localizer of BRCA2)
Encodes a protein involved in DSB repair by binding and localizing with BRCA2. PALB2 binds the single strand DNA and directly interacts with the recombinase RAD51, an important step in homologous recombination. There is preclinical and clinical evidence (in prostate cancer) of PALB2 sensitivity to PARP inhibition43,44.

POLD1 (Polymerase Delta 1)
Encodes the catalytic subunit of Pol $^{\delta}$ which has a role in DNA DSB repair via HR45.

PRKDC (Protein Kinase, DNA-Activated, Catalytic Polypeptide)
Encodes the protein DNA-PK (DNA-dependent protein kinase) which belong to the PI3-kinase family. The enzyme is required for non-homologous end joining (NHEJ) DNA DSB repair 46. Phosphorylation of substrates by DNA-PK induces recruitment of DSB proteins and activation of checkpoints 47. Synthetic lethality involving DNA-PK loss and various DDR proteins (e.g. ATM) has been observed in preclinical studies 48.

PTEN (Phosphatase and Tensin Homolog)
Encodes protein that is a potent tumor suppressor. It is the central negative regulator of the PI3K/AKT pathway. Loss of PTEN causes increased AKT activation causing cellular proliferation49. PTEN interacts with RAD51 and RAD54 to assist in DNA DSB repair and homologous recombination. There is preclinical data of PTEN mutated cell lines exhibiting synthetic lethality when exposed to a PARP inhibitor50.

RAD50
Encodes protein which helps form MRN complex which is involved in detection and repair of DNA DSB42.

RAD51
Encodes protein that is one of five paralogs of RAD51 (RAD51B, RAD51C, RAD51D, XRCC2 and XRCC3). The paralogs are all required for DNA DSB repair. BRCA1/2, PALB2 and PTEN help RAD51 assembly on ssDNA, a key step in DNA DSB repair via HR51,52.

RAD52
Encodes protein that is involved in DNA DSB repair, specifically the 5’ to 3’ resection phase, via interaction with RPA and RAD51.

RAD54
Encodes protein is a critical protein involved in HR, specifically branch migration and new DNA synthesis. It interacts with RAD51 to help stimulate DNA strand exchange53.

RPA1 (Replication Protein A1)
Encodes protein that is involved in all modes of DNA repair. As it pertains to DSB repair, RPA interacts with RAD51 and RAD52 to assist in 5' to 3' resection and strand invasion. There is also evidence of interaction with BRCA1 and BRCA254.

SLX4
Encodes protein that forms a multiunit complex involved in DNA DSB repair. This complex promotes cleavage of Holliday junctions at replication forks for single stranded annealing55.

WRN (Werner Syndrome Helicase)
Encodes protein that unwinds and separates DS DNA. The enzyme interacts with RAD51 to assist with DSB (HR, NHEJ) and BER repair56,57.

XRCC
A family of genes whose proteins are integrally involved in DSB DNA repair. XRCC2 and XRCC3 form complexes with RAD51 to assist in HR. XRCC11 interacts with BRCA2 to assist in HR. XRCC4 has direct interaction with LIG4 to assist in DSB ligation via NHEJ. XRCC5, XRCC6, and XRCC7 are involved in NHEJ by interacting with DNA-PK58.

1.2 Background of Niraparib

Niraparib is an orally active PARP 1/2 inhibitor which targets tumors with defects in the HR repair pathway or tumors that are driven by PARP-mediated transcription factors. Niraparib demonstrates selective anti-proliferative activity for cancer cell lines that have been silenced for BRCA-1 or BRCA-2 (or carry the mutation) compared to wild-type cell line. Niraparib causes cell cycle arrest in G2/M followed by apoptosis. The drug is also cytotoxic when evaluated in small cell lung cancer cell lines carrying homozygous inactivation of the ataxia telangiectasia mutated gene. In vivo studies demonstrated anti-tumor activity with BRCA-1 mutant breast cells, BRCA-2 mutant pancreatic cancer, serous ovarian cancer, and xenograft models in mice.

1.3 Safety of Niraparib

Niraparib has low potential for drug-drug interactions in humans because it is a substrate of multiple metabolic enzymes including the significant involvement of the non-CYP (cytochrome P450) enzymes (i.e., carboxylesterases [CEs] and UDP-glucuronosyltransferases [UGTs]).

There is phase 1, 2, and 3 data showing safety for niraparib. A Phase 1 clinical trial revealed the dose-limiting toxicity (DLT) for niraparib at 400 mg daily was thrombocytopenia59. The maximum tolerated dose (MTD) was determined to be 300 mg daily. Drug-related toxicities at 300 mg, were grade 1-2 (reversible), and included: anemia (48%), fatigue (42%), nausea (42%), thrombocytopenia (35%), anorexia (27%), neutropenia (24%), constipation (23%), and vomiting (20%).

In the published phase 3 trial of ovarian cancer patients with niraparib the drug was found to be safe and tolerable60. Toxicities were very manageable with the most common grade 3 or 4 toxicities being, thrombocytopenia (33.8%), anemia (25.3%), neutropenia (19.6%), and hypertension (8.2%). Overall, 14.7% subjects who received niraparib discontinued the drug because of an adverse event. Most of the hematologic laboratory parameters occurred within the first three treatments. Treatment discontinuations were rare due to hematologic toxicity (Table 1).

Table 1: Treatment Discontinuation Due to Myelosuppression Adverse Events of Any Grade

Event	Niraparib (N=367)	Placebo (N=179)
	no (%)	no (%)
Thrombocytopenia	12 (3.3)	1 (0.6)
Neutropenia	7 (1.9)	0
Leukopenia	7 (1.9)	0
Anemia	5 (1.4)	0
Pancytopenia	3 (0.8)	0

1.4 Efficacy of Niraparib

In preclinical models, niraparib has been observed to inhibit normal DNA repair mechanisms and induce synthetic lethality when administered to cells with HR defects. In a BRCA1 mutant xenograft study, niraparib dosed orally caused tumor regression which was accompanied by >90% reduction in tumor weight compared to control. In a BRCA2 mutant xenograft study, niraparib dosed mice showed 55-60% growth inhibition, both by tumor volume and weight. Niraparib is also selectively toxic for tumor cell lines carrying homozygous activation of the ATM gene. Details can be found in the Investigator's Brochure.

Anti-tumor activity was observed in the phase I studies taking niraparib as monotherapy at dose levels ranging from 60 to 400 mg. An overall response rate of 13% was observed for all subjects

in this study. Analysis of the 20 BRCA-mutant ovarian cancer patients showed a 35% overall response rate.

A phase 3 randomized, double blind trial evaluated the efficacy of niraparib at 300 mg orally daily versus placebo as a maintenance treatment for subjects with platinum-sensitive, recurrent ovarian cancer60. Subjects were categorized according to the presence or absence of a germline BRCA mutation and then subsequently randomized to niraparib 300 mg orally or placebo in a 2:1 fashion. Results revealed improved PFS in both the BRCA mutated group (21 vs 5.5 months) and non-BRCA group (9.3 vs 3.9 months). We will be using the same 300mg daily dose in our study.

1.5 Overview of Non-Clinical Studies

In non-clinical study models, niraparib treatment-related effects were observed (see Section 4.3 of the Investigator's Brochure Version 6.1). Niraparib was not considered mutagenic in Ames test, but was positive in 3 other genotoxicity assays (assay for DNA strand breaks in rat hepatocytes, CHO chromosomal aberrations assay and in vivo micronucleus assay of bone marrow cells).

In the dog model, decreases in hematology values were observed during dosing, which resolved by the end of recovery. In the rat, mortality at the highest dose tested was considered to be due to septicemia likely due to cellular depletion of lymphoid organs and bone marrow.

1.6 Overview of Clinical Studies

An overview of clinical studies conducted for niraparib can be referenced in Table 2. For more details refer to the Investigator's Brochure.

1.6.1 Phase 1 Trials

Niraparib has been administered to 144 patients in the Phase 1 program. The most commonly reported (>20.0%) AEs (all grades, n = 144), were fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), and leukopenia (20.8%).

The MTD was determined in Part A of Study PN001 to be 300 mg QD. Of note, the dose limiting toxicity of Grade 4 thrombocytopenia was observed in 2/6 subjects treated at the 400 mg QD dose level. Additionally, 1 subject had a DLT of Grade 3 fatigue (30 mg QD) and 1 subject had a DLT of Grade 3 pneumonitis (60 mg QD). The subject who experienced pneumonitis had breast cancer involving the chest wall and had received prior radiation therapy, which involved exposure of lung to radiation. The pneumonitis did not have the sharp border representing the prior radiation port typical of recall pneumonitis. Since PARP inhibitors potentiate radiation damage in

nonclinical models when given concurrently, it is possible that a PARP inhibitor could induce recall radiation pneumonitis. Two other subjects with breast cancer involving the chest wall who had received prior radiation therapy were subsequently treated and had no evidence of pneumonitis.

In PN001, 21 subjects treated at the MTD had AEs of thrombocytopenia reported (9 subjects Grade 1, 5 subjects had Grade 2, 4 subjects had Grade 3, and 3 subjects had Grade 4), 16 subjects experienced neutropenia (7 subjects Grade 1, 5 subjects Grade 2, and 4 subjects Grade 3), and 34 subjects experienced anemia (5 subjects Grade 1, 21 subjects Grade 2, and 8 subjects Grade 3).

1.6.2 Phase III Trial

In the published Phase 3 trial 31 utilizing single agent niraparib, the most common (>20%) AEs were nausea (73.6.0%), thrombocytopenia (61.3%), fatigue (59.4%), anemia (50.1%), constipation (39.8%), vomiting (34.3%), neutropenia (30.2%), headache (25.9%), decreased appetite (25.3%), insomnia (24.3%) and abdominal pain (22.6%). The most common (>10%) grade 3 or 4 AEs were thrombocytopenia (33.8%), anemia (25.3%) and neutropenia (19.6%). No subjects had a grade 3 or 4 bleeding event. Thrombocytopenia was transient and platelet levels stabilized beyond cycle 3.

Table 2: Overview of Clinical Studies of Niraparib

Protocol Number	Study Title	Status
Phase 1		
PN001	A Phase 1 Study Of Niraparib In Patients With Advanced Solid Tumors Or Hematologic Malignancies	Completed
PN005	A Phase 1 Study Of Niraparib In Patients With Solid Tumors	Terminated
PN008	A Phase 1b Dose Escalation Study Of Niraparib In Combination With Carboplatin, Carboplatin/Paclitaxel And Carboplatin/Liposomal Doxorubicin In Patients With Advanced Solid Tumors	Terminated
PN011	A Phase 1b Dose Escalation Study Of Niraparib In Combination With Pegylated Liposomal Doxorubicin (Doxil™ Or Caelyx™) In Patients With Advanced Solid Tumors With A Cohort Expansion In Patients With Platinum-Resistant/Refractory High Grade Serous Ovarian Cancer.	Terminated

Protocol Number	Study Title	Status
PN014	A Phase 1 Study Of Niraparib In Combination With Temozolomide (TMZ) In Patients With Advanced Cancer	Completed
PR-30-5015-C AME	Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer	Ongoing
64091742PCR1001	A Safety and Pharmacokinetics Study of Niraparib Plus Androgen Receptor-Targeted Therapy (Apalutamide or Abiraterone Acetate Plus Prednisone) in Men With Metastatic Castration-Resistant Prostate Cancer	Ongoing
Phase 1/2		
3000-PN162-01-001	Phase 1/2 Clinical Study of Niraparib in Combination With Pembrolizumab in Patients With Advanced or Metastatic Triple-Negative Breast Cancer and in Patients With Recurrent Ovarian Cancer	Ongoing
Phase 2		
PR-30-5020-C	A Phase 2, Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Niraparib in Patients With Advanced, Relapsed, High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Have Received Three or Four Previous Chemotherapy Regimens	Ongoing
64091742PCR2001	A Phase 2 Efficacy and Safety Study of Niraparib in Men With Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies	Ongoing
Phase 3		
PR-30-5010-C BRAVO	A Phase III, Randomized, Open Label, Multicenter, Controlled Trial of Niraparib Versus Physician's Choice in Previously-Treated, HER2 Negative, Germline BRCA Mutation-Positive Breast Cancer Patients	Ongoing
PR-30-5011-C	A Phase 3 Randomized Double-Blind Trial of Maintenance With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer	Ongoing
PR-30-5011-C1- QTC	QTc Sub-Study: A Phase 3 Randomized Double-Blind Trial of Maintenance With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer	Ongoing

Protocol Number	Study Title	Status
PR-30-5017-C PRIMA	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy	Ongoing
PR-30-5011-C2-FE	FE Sub-Study: A Phase 3 Randomized Double-Blind Trial of Maintenance With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer	Completed

1.7 Rationale for Regimen/Doses/Schedule

An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase I study, PN001. This analysis determined that only baseline platelets had an impact on platelet nadir; lower baseline platelets (<180 109/L) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76%) or Grade ≥ 3 (45%) compared to subjects 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 (subjects with a body weight less than 58 kg at baseline) compared to the highest quartile (subjects with a body weight greater than or equal to 77 kg at baseline). While TEAEs (added to list of abbreviations) occurred in most subjects 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 subjects with a body weight <58 kg, approximately 80% of subjects had a dose reduction compared to 59% of subjects with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24%) compared to subjects 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 subjects 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 subject developing ≥Grade 3 thrombocytopenia within 30 days after the first dose of niraparib. The results of the model show that the subgroup of subjects with a baseline body weight <77 kg or baseline platelet count <150,000 µL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of subjects 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 subjects with a body weight >77 kg and platelet count >150,000 µL, and was only 206 mg for subjects with body weight < 77 kg or platelet count <150,000 µL. Thus, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. These observations are to be confirmed in the present study with the inclusion of study treatment dosed at 200 mg (2 capsules of niraparib or placebo) in subjects whose baseline weight is <77 kg or baseline platelet count is <150,000 µL.

The current clinical dose of 300 mg daily (dry-filled capsules) was determined to be the MTD in early clinical testing (as above). This was also the dose given in the (490-subject) phase 3 randomized, double-blind, placebo-controlled trial (see toxicity above). Based on the above data subjects with weight < 77 kg or have a platelet count of < 150,000 µl in this trial will start at the 200 mg daily dose.

2. OBJECTIVES

2.1 Primary

- To determine the objective response rate (ORR) for subjects with BAP1 and other DDR repair pathway deficiencies treated with niraparib.

2.2 Secondary

- To determine the median progression free survival (PFS) and estimate PFS at 3 and 6 months in each cohort and histologic subsets of subjects. PFS is defined as the duration of time from study entry to time of progression or death or the date of last contact, whichever occurs first.
- To estimate the median overall survival (OS)
- To determine the incidence, severity, and reversibility of toxicities in subjects treated with niraparib.

2.3 Exploratory

- To explore the impact that specific DNA repair mechanism deficiencies have on tumor PARP inhibition
- To explore alternate biomarkers that predict response to PARP inhibition

3. STUDY DESIGN

3.1 Study Overview

This is a prospective, open-label phase II trial in two biologically distinct patient cohorts. A total of 47 subjects are planned. Each subject will be administered a daily dose of study drug during treatment cycles. Each cycle is twenty-eight (+/- 1) days in length. Study treatment will continue until the development of unacceptable toxicity, disease progression (radiographic assessment every 8 weeks), or participant desire to discontinue protocol therapy. Clinic evaluations will be

taken at baseline, days 1 and 15 for the first cycle, and day 1 of each subsequent cycle (28 +/- 1 days). Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following treatment regimen will be used:

- Both subject cohorts A and B will receive niraparib at 300 mg orally daily on each day of twenty-eight (+/-1) day cycle.
- Enrolled study participants will continue on study for approximately 8 weeks, unless otherwise clinically indicated, before tumor status is assessed radiographically. Total study duration is dependent on imaging studies (i.e. stable disease, progression, or response) and/or subject tolerability of study drug.

4. SELECTION OF SUBJECTS

Subjects with a diagnosis of incurable cancer who meet the following inclusion and exclusion criteria will be eligible for participation in this study. In the event of a known BAP1 mutation in a histology included in Cohort A, assignment would be to Cohort A as BAP1 status will be eventually determined post-hoc.

4.1 Number of Subjects

A total of 47 subjects are to be enrolled with thirty-five subjects in Cohort A and twelve subjects in Cohort B. Additionally, there is the possibility of further subject enrollment (a pre-specified optional expansion cohort of up to an additional 20 subjects [to obtain 18 evaluable]) based on meeting a minimum ORR in each specific histology identified in Cohort A (See Section 12.1).

4.2 Inclusion Criteria

Individuals eligible for study participation must meet the following criteria:

A. Must be ≥ 18 years of age
B. A clinical diagnosis of incurable cancer confirmed histologically.
C. (For Cohort A) Must have confirmed diagnosis consistent with uveal melanoma, mesothelioma, renal cell carcinoma (clear cell subtype), or cholangiocarcinoma.
D. (For Cohort B) Must have a pre-specified DNA damage repair mutation including any one of the following: ARID1A, ATM, ATR, BACH1 (BRIP1), BAP1, BARD1, BLM, CHEK1, CHEK2, CDK2, CDK4, ERCC, FAM175A, FEN1, IDH1, IDH2, MRE11A, NBN (NBS1), PALB2, POLD1, PRKDC (DNA-PK), PTEN, RAD50, RAD51, RAD52, RAD54, RPA1, SLX4, WRN, or XRCC. Only CLIA certified next generation sequencing (NGS) assays are acceptable. Variants of unknown significance (VUS) will be allowed to enroll on study. Cohort B enrollment is histology agnostic.

E. Must have formalin-fixed paraffin embedded (FFPE) tissue available for research purposes. Tissue must have been obtained within the last 3 years from a core or excisional biopsy.
F. Measurable disease by RECIST (v 1.1) criteria (prior radiation therapy to any indicator lesion must have demonstrated progressive growth of the lesion to be considered measurable).
G. Adequate organ function as defined as:
   - Absolute neutrophil count (ANC) ≥ 1,500/µL
   - Hemoglobin ≥ 9g/dL
   - Platelets ≥ 100,000/µL
   - Total bilirubin ≤ 1.5 ULN or direct bilirubin ≤ 1 x ULN
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN; if liver metastases present, then AST and ALT must be ≤ 5 x ULN
   - Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min using Cockcroft-Gault equation
H. A medical history with prior exposure to standard systemic therapy (having exhausted or declined all known and currently approved effective life prolonging therapies).
I. An ECOG Performance Status less than or equal to 1.
J. A life expectancy of greater than or equal to 12 weeks
K. Written informed consent obtained from the subject and the ability for the subject to comply with all the study-related procedures.
L. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 7 days prior to the first dose AND be using an adequate method of contraception to avoid pregnancy throughout the study and for at least 180 days after the last dose of study drug to minimize the risk of pregnancy. An adequate method of contraception is defined as contraceptive methods with a failure rate of less than 1% per year when used consistently and correctly. Subjects and their sexual partners who have undergone vasectomy or tubal occlusion must also use a male condom with spermicide. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.
   WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopausal defined as: Amenorrhea that has lasted for 12 consecutive months without another cause, or for women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL.
M. Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (e.g., abstinence, condoms, vasectomy) throughout the study and should avoid conceiving children for 180 days following the last dose of

study drug. In addition, men must not donate sperm during niraparib therapy and for 180 days after receiving the last dose of niraparib.

N. Subjects must agree to not donate blood during the study or for 90 days after the last dose of study treatment.
O. Subjects receiving oral corticosteroids may continue as long as their dose is stable for least 4 weeks prior to initiating protocol therapy.
P. If a new biopsy is needed for diagnostic reasons, the biopsy must be performed from a tumor site that is not the only site of measurable disease.

4.3 Exclusion Criteria

Subjects with any of the following will not be eligible for study participation:

A. A medical history of prior exposure to PARP inhibitors (olaparib, niraparib rucaparib, etc.).
B. Subject has received or is planning to receive live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial.
C. A medical history demonstrating a BRCA1 or BCRA2 mutation.
D. A pathologic diagnosis of prostate cancer as the cancer to be treated in cohort B.
E. Subject is simultaneously enrolled in any other interventional clinical trial.
F. Subject has had major surgery ≤ 3 weeks of enrollment, and subject must have recovered from any effects of any major surgery.
G. Subject has 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.
H. Subject has had radiotherapy encompassing > 20% of the bone marrow within 4 weeks of the first dose.
I. Subject has a known hypersensitivity to the components of niraparib or the excipients.
J. Subject received a transfusion (platelets or red blood cells) ≤ 4 weeks of the first dose of study treatment.
K. Subject has 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.
L. Subject has more than one active malignancy at the time of enrollment (Subjects with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen [as determined by the treatment physician and approved by the PI] may be included).
M. Subject has known, active symptomatic brain or leptomeningeal metastases.
N. Subject has had any known Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment.

O. Subject has any known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).
P. Females or males of childbearing potential who are unwilling or unable to use an acceptable method of birth control to avoid pregnancy for the entire study period and for at least 180 days after the last dose of study drug.
Q. Females who are pregnant or breastfeeding.
R. History of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician or study PI.
S. Prisoners or subjects who are involuntarily incarcerated.
T. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness.
U. Subjects demonstrating an inability to comply with the study and/or follow-up procedures.

4.4 Inclusion of Women and Minorities

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

5. REGISTRATION PROCEDURES

All consented subjects must entered into the University of Florida's Clinical Trial Management System (OnCore) prior to assignment of a subject identification number. This is not registration into the trial. The study team must submit the completed study specific eligibility checklist, supporting source documentation and a copy of the signed informed consent document(s) to the UFHCC Project Management Office (PMO; PMO@cancer.ufl.edu) or their assigned Project Manager. Unsigned eligibility checklists or eligibility packets with missing or incomplete information may be returned to the study team. Upon receipt of a completed eligibility packet, the designated Project Manager will review the source to verify eligibility and assign a subject number. If eligibility cannot be confirmed, the project manager will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be able to participate in the trial.

6. STUDY PROCEDURES

Please see the Schedule of Events located in Appendix A.

6.1 Screening Evaluations (Days -21 to Day 0):

Written informed consent must be obtained prior to performing any study-specific evaluations or tests. Tests or evaluations performed as standard of care within the specified screening period, but prior to informed consent, may be accepted for this study and need not be repeated.

The following pre-treatment measurements will be obtained within 21 days prior to the initiation of study therapy:

- Height, weight and ECOG performance will be collected from each subject.
- A complete medical history, toxicity assessment, and physical exam will be completed for each subject.
- Blood and urine samples will be obtained for the following laboratory studies:
    - CBC with differential count
    - Comprehensive metabolic panel
    - Urine or serum pregnancy test (females of potential child-bearing status only)
- CT or PET/CT scans, or MRI scans of the chest, abdomen, and pelvis will be obtained for tumor measurement (NOTE: baseline study imaging must be performed within 28 days prior to initiation of study therapy). Imaging studies used at study entry to establish baseline tumor measurement(s) should be the imaging modalities used to monitor subsequent disease response.
- Attainment and submission of previously obtained FFPE tissue (must have been obtained within last 3 years). If archival tissue is unavailable or inadequate, new biopsy must be obtained to confirm histology and molecular profile.

6.2 Baseline Treatment Evaluations (Day 1, Cycle 1):

- Height, weight and ECOG performance will be collected from each subject.
- An interim medical history, toxicity assessment, and physical exam will be obtained from each subject.
- Blood and urine samples will be obtained for the following laboratory studies:
    - CBC with differential count (Note: CBCs should be collected weekly during Cycle 1.
    - Comprehensive metabolic panel
    - Urine or serum pregnancy test (females of potential child-bearing status only)
    - Research blood collection

6.3 On-Treatment Evaluations (Day 15 ± 1 day, Cycle 1):

- Height, weight and ECOG performance status will be collected from each subject.
- An interim medical history, toxicity assessment, and physical exam will be obtained from each subject.
- Blood samples for a CBC with differential count and a comprehensive metabolic panel will be obtained.
- Research blood collection

6.4 On-Treatment Evaluations (Day 1 ± 1 day, Cycle 2 and every cycle following):

- Height, weight and ECOG performance will be collected from each subject.
- An interim medical history, toxicity assessment, and physical exam will be obtained from each subject.
- Blood and urine samples will be obtained for the following laboratory studies:
    - CBC with differential count
    - Comprehensive metabolic panel
    - Urine or serum pregnancy test (females of potential child-bearing status only)
    - Research blood collection
- Repeat imaging will be obtained every 8 weeks (+/- 7 days) from first dose (Cycle 1 Day 1) until disease progression or death to assess response.

6.5 End of Treatment (EOT) Evaluations (within seven days of last study drug administration):

- Height, weight and ECOG performance status will be collected from each subject.
- An interim medical history, toxicity assessment, and physical exam will be obtained from each subject.
- Blood will be obtained for the following laboratory studies:
    - CBC with differential count
    - Comprehensive metabolic panel
    - Research blood collection
- A tumor biopsy will be done upon progression of disease (with subject's permission) for research purposes. The timing of the research biopsy should be ideally within 7 days of the EOT visit or at least prior to the start of any subsequent anticancer therapy.
- If feasible, the EOT visit, except for the biopsy noted in 6.5, should be performed within seven days regardless of the reason for discontinuation. If the subject withdraws consent, however, no further study procedures can proceed.

6.6 Follow-up Evaluations (30 ± 3 days post EOT):

- Height, weight and ECOG performance status will be collected from each subject.
- An interim medical history, toxicity assessment, and physical exam will be obtained from each subject.
- Blood samples for a CBC with differential count and a comprehensive metabolic panel will be obtained.
- Research blood collection.

Follow-up Evaluations should occur regardless of the reason for discontinuation. If the subject withdraws consent, however, no further study procedures can proceed.

Subjects will additionally be followed every three months for vital statistics and development of MDS/AML until death. If subjects are lost to follow-up, every effort will be made at least quarterly to attempt to locate the subject to obtain their health status.

6.7 Unscheduled Evaluations for Adverse Events:

- An interim medical history, toxicity assessment, and physical exam will be obtained.
- Blood will be obtained for laboratory evaluation at the treating physician's discretion to support clinical workup.
- If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC also will be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume.
- If the chest CT or MRI is clear at screening, repeat chest imaging is not required in the absence of lesions to be followed or in the absence of clinical indication requiring follow-up; otherwise, repeat chest imaging should be completed at the same time as RECIST imaging.
- For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Principal Investigator. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization criteria) and other sample testing reports related to MDS/AML. The site must keep a copy of the report with the subject's study file.

7. STUDY TREATMENT

All subjects entering the screening phase will receive a unique subject number. This number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number.

7.1 Treatment Schedule/Administration

Niraparib will be administered as a flat-fixed, continuous daily dose beginning at the baseline visit (Cycle 1/Day 1) according to the Table 3 below.

Table 3: Niraparib Dosing

Baseline Criteria (weight and platelet count)	**Starting Dose**
≥77 kg and platelets ≥150,000 µL	300 mg (3 X 100 mg capsules)
<77 kg or platelets 100, 000 -149,000 µL	200 mg (2 X 100 mg capsules) *

*For subjects whose starting dose is 2 capsules once daily, escalation to 3 capsules once daily is required at the discretion of the treating provider at the beginning of cycle 3 ± 1 day, if no treatment interruption or discontinuation was required during the first 2 cycles of therapy, and the treating physician documents no other justification to maintain the lower dose.

If tumor assessment done with diagnostic imaging demonstrates a decrease (i.e. partial response) or no change in tumor size (i.e. stable disease), subjects may continue on this niraparib regimen.

7.2 Specific Supportive Care

7.2.1 Concomitant Therapy

Relevant medical history should be obtained at screening and include prior medications and treatment history. All medications taken within four weeks (or 28 days) prior to screening, regardless of indication, should be recorded.

Any therapy or medication (except study drugs), administered from screening until thirty days after the last dose of either study drug, is considered a concomitant therapy or medication. However, if another course of anti-cancer therapy is initiated prior to the thirty -day follow-up period visit; a record of concomitant medications will no longer be performed. If the use of any concomitant treatments (medications or procedures) becomes necessary, the treatment must be recorded, including the name of the drug or treatment, dose, route, date, indication for use,

expected duration, and frequency of treatment. Assessment and documentation of concomitant medications will be done at each visit.

7.2.2 Allowed Concomitant Therapy

See protocol-specific supportive care information in Section 7.2. All other supportive measures consistent with optimal patient care will be given throughout the study.

- Nausea: Anti-emetics should be administered per institutional guidelines.
- Diarrhea: Subjects should be provided with instructions on use of loperamide (Imodium) in the event of diarrhea, as well as instructions to contact the treating physician. Other anti-diarrheals are also allowed. Subjects should be given mouth care instructions per institutional guidelines.
- Neutropenia: Prophylactic use of G-CSF or Peg-G-CSF is not permitted. Please refer to Table 4 for neutropenia adverse event guidelines.

7.2.3 Prohibited Concomitant Therapy

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than the study drug in this trial
- Radiation therapy Radiation Therapy
- Palliative radiation therapy (excluding the pelvic region and/or palliative radiotherapy encompassing > 20% of the bone marrow within 2 weeks of the first dose of study treatment) to a symptomatic solitary lesion may be considered on an exceptional case by case basis 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 after consultation with sponsor-investigator. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- Vaccines
    - Live vaccines are prohibited within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine.
    - Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines, and are not allowed.

- Substrates of P-glycoprotein
    - Niraparib is a substrate for P-glycoprotein (P-gp); therefore, subjects should be advised to use caution with drugs that are inhibitors of P-gp. The niraparib safety profile includes risk for thrombocytopenia; therefore, subjects should be advised to use caution with anticoagulation and antiplatelet drugs.
- Blood Donation
    - Subjects must not donate blood during the study or for 90 days after the last dose of study treatment.

7.3 Dose Modifications

Treatment must be interrupted for any non-hematologic National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.03, http://evs.nci.nih.gov/ftp1/CTCAE/About.html) grade 3 or 4 adverse event which the Investigator considers related to the administration of niraparib. If toxicity is appropriately resolved to baseline or grade 1 or less within 28 days, the subject may restart treatment with niraparib, but with a dose level reduction according to Table 5. If event recurs at similar or worse grade, treatment should be interrupted again and upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted.

If the toxicity requiring dose interruption has not resolved completely or to NCI-CTCAE grade 1 during the maximum 4-week (28 day) dose interruption period, and/or the subject has undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg once daily), the subject must permanently discontinue treatment with niraparib.

For subjects whose 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.

Table 4: Niraparib 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
If initial starting dose was 200 mg/day but subsequently increased to 300 mg/day at cycle 3, dose reductions are to follow as if they started at 300 mg/day.		

7.3.1 Non- Hematologic Toxicity

Table 5: Niraparib Dose Modifications for Non-Hematologic Toxicities

Event	**Dose**
Non-hematologic CTCAE ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	• Withhold niraparib for a maximum of 28 days or until adverse reaction has improved to < Grade 1. • Resume niraparib at a one dose level reduction per Table 4.
CTCAE ≥ 3 treatment-related adverse reaction lasting more than 28 days while subject is administered niraparib 100 mg/day	Discontinue niraparib

7.3.2 Hematologic Toxicity

Table 6: Niraparib Dose Modifications for Hematologic Toxicities*

Event	Dose Modification
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:** If platelet count is 75,000-100,000/µL: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL*** • Resume niraparib at same or reduced dose per Table 4 If platelet count is < 75,000/ µL: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL*** • Resume niraparib at a reduced dose. **Second occurrence:** • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL.*** • Resume niraparib at a reduced dose per Table 4.
Neutrophils < 1,000/ µL or	Withhold niraparib for a maximum of 28 days and monitor

Hemoglobin < 8 g/dL	blood counts weekly until neutrophil counts return to ≥ 1,500/µL or hemoglobin returns to ≥ 9 g/dL***. Resume niraparib at a reduced dose per Table 4
Hematologic adverse reaction requiring transfusion	For subjects with platelet count ≤ 10,000/µL, platelet transfusion should be considered. If there are other risk factors such as co- administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Resume niraparib at a reduced dose.
Confirmed diagnosis of MDS* or AML†	Permanently discontinue niraparib.
*MDS = myelodysplastic syndrome †AML = acute myeloid leukemia	

*Dose reduction table to be followed regardless of timing of hematological toxicity
**If MDS or AML is confirmed, discontinue niraparib.
*** Discontinue niraparib if the platelet count, neutrophils and/or hemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the subject has already undergone dose reduction to 100 mg once daily.***

If a dose modification is required at any point on study due to hematologic toxicity, to ensure safety of the new dose, weekly blood draws for CBC will be required for an additional four weeks after the AE has been resolved to the specified levels, after which monitoring every four weeks may resume. If the hematologic toxicity has not recovered to the specified levels within four weeks (28 days) of the dose hold and/or the subject has already undergone a maximum of two dose reductions (to a minimum dose of 100 mg daily), then the subject will permanently discontinue treatment with niraparib.

Any subject requiring transfusion of platelets or red blood cells must undergo a dose reduction upon recovery if study treatment is resumed. Growth factors are allowed, but do not negate the requirement for dose reductions. Continuation of growth factors for all subsequent cycles is allowed but at the discretion of the treating physician.

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

For surgery while on treatment, up to 28 days of study treatment interruption is allowed. Once the dose of study treatment has been reduced, any re-escalation must be discussed with the study PI.
All dose interruptions and reductions (including any missed doses), and the reasons for the

reductions/interruptions, are to be documented in the subject's study file.

7.4 Supportive Care Guidelines

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, antidiarrheals, analgesics, etc., when appropriate. Bisphosphonates or denosumab are allowed for subjects with bone metastases.

7.5 Other Considerations

Special consideration and caution should be given for subjects with previous radiation to the chest wall and/or lungs given report of pneumonitis with niraparib. This reported toxicity was thought to be secondary to radiation recall from previous radiation exposure to the lungs.

8. TREATMENT DISCONTINUATION

8.1 Removal of Subjects from Study

Subjects who discontinue participation in the clinical study on their own or subjects who are withdrawn by the investigator, for reasons other than completion of treatment, disease progression or toxicity, will be defined as premature withdrawals.

Subjects who are not initiated on study drug, but sign informed consent and undergo at least some of the screening procedures will be considered screening failures. A record of these subjects will be maintained by the study site.

8.2 Criteria for Study Treatment Discontinuation

A subject will be discontinued from protocol therapy under the following circumstances:

- Any cancer therapy or new cancer-directed medication (except study drugs), administered from screening until thirty days following EOT.
- Any adverse event which, in the Investigator's opinion, requires termination of the study medication.
- Disease progression, unless at the discretion of the principal investigator (in collaboration with any co-sponsors or collaborators) continued treatment with study drug is appropriate.
- Substantial non-compliance with the requirements of the study.
- The subject presents with a beta-HCG test consistent with pregnancy. Pregnancy will be reported along the same timelines as a serious adverse event.
- The subject uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise

interfering with results.
- The development of a second malignancy that requires treatment, which would interfere with this study.
- The subject is lost to follow-up.
- Interruption in study drugs administration for greater than twenty-eight days (see Dose Modification section).
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a significant degree.
- Subject desire to discontinue therapy.

The Investigator will make every reasonable effort to keep each subject in the study unless it is in the subject's best interests to discontinue participation. If a subject is removed from the study or declines further participation, all EOT evaluations should be performed if the subject is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all subjects are followed up for survival status after the Final Visit.

Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all subjects participating in the study, even for a brief period of time. Subjects who discontinue following entry will have relevant information completed and recorded on the CRF. All subjects who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any subject should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the UF Health Data Integrity and Safety Committee and the UF IRB as outlined in Section 11.4.

8.3 Replacement of Subjects

Subjects who do not receive any doses of study drug will be replaced. Subjects who receive any dose of study drug will contribute to safety and toxicity data, but will be replaced if they cannot provide response assessment due to study discontinuation for reasons other than disease progression or toxicity.

9. BIOLOGICAL SPECIMENS AND CORRELATIVES

9.1 Source of Specimens

Blood, serum, and plasma will be collected at different time points for study evaluations. All specimens collected as part of this study will be labeled with a study-specific ID number distinct from their personal information. A master code key that links specimen ID with subject identifiers

will be maintained in a restricted section of OnCore available only to the PI or approved study team delegates. A core needle (or excisional) biopsy must have been obtained within 3 years of study enrollment. If a new biopsy is obtained for diagnostic reasons, the biopsy must be performed from a tumor site that is not the only site of measurable disease. For subjects with only one site of measurable disease, biopsies from that site will be allowed if CT imaging performed after biopsy still shows measurable disease and/or the biopsy is not expected to impact the measurability of the lesion. Discussion with the PI prior to biopsy is recommended.

9.2 Tumor Analysis and Molecular Profiling

For tumor analysis, a tumor block is preferred. As a substitute, 12 unstained slides are required. It is preferred that normal and tumor tissue be represented on the slide. This will be obtained for all archive tissue pre-treatment as well as any subject undergoing optional biopsy at end of treatment.

9.3 Next Generation Sequencing

Next Generation Sequencing (NGS) results are not required for enrollment in cohort A. If they are available from a CLIA-approved lab, results will be recorded in the CRF. Histologic tumor type will take priority over molecular profile if a conflict arises between potential cohort assignments.

For cohort B, subject enrollment will be histology agnostic, but based on the presence of somatic molecular abnormalities involving any component of the DNA damage repair pathway, including: BAP1, PALB2, ATM, ATR, RAD51, RAD54, XRCC, ERCC, BLM, BARD, FANCD2, PTEN, IDH1/IDH2 or BACH. NGS results will be permitted from any clinical or commercial vendor so long as the assay is from a CLIA certified lab. Variants of unknown significance (VUS) are allowable for enrollment. Mutations involving BRCA (1 or 2) are NOT allowed on this study. A histology of prostate cancer is NOT allowed on this study.

9.4 Correlative Studies

The following table represents some of the proposed correlative analyses associated with this trial. Collection of biospecimens will allow these and/or other analyses to take place in a pre-planned, but post-hoc manner. Alternative sources of funding will be leveraged to perform these correlative analyses. Additional testing and hypothesis generating studies may be undertaken at the discretion of the study team. HRD assay will be chosen at the end of study enrollment but will be a commercial CLIA approved test (e.g., Myriad myChoice®). Only genetic tests that are obtain by the treating physician as part of routine clinical care will be disclosed to the subject by the treating physician. No genetic test results from the correlative analyses in this study will be disclosed. Exploratory assessment of mutations may involve both somatic (tumor) and germline (blood) analyses.

Table 7: Correlative Assessments by Cohort

Cohort A Only	Both Cohorts	Cohort B Only
BAP1 IHC on tumor tissue BAP1 gene sequencing Assessment of additional mutations of the DNA DSB repair pathway via NGS that enhance or impede BAP1 as a predictor of PARPi activity.	Exploring alternative biomarkers that could predict response (i.e. homologous recombination deficiency score) to PARP inhibition BAP1 gene sequencing Exploratory assessment of circulating biomarkers of response (i.e. peripheral immunome, circulating tumor DNA) Tumor biopsy upon progression in subset of subjects to explore mechanisms of resistance to PARP inhibition including, but not limited to, BRCA overexpression and/or alternate activation of HR pathway	Cross-referencing mutations with known databases (retrospectively) to evaluate whether germline or somatic in origin Determination of previously undocumented VUS as predictors of PARPi activity

9.2 Preparation, Shipment and Storage of Specimens

Refer to the Study Procedure Manual for collection, processing and shipping instructions for all tissue and blood specimens.

Formalin-fixed paraffin-embedded tumor tissue must be submitted prior to start of study drug. A tissue block or minimum of 12 slides is required. Tissue must have been obtained via routine care within 3 years of study enrollment or new specimens are required to be collected. Blood collected will be processed to isolate DNA and RNA for future potential genetic analyses.

All blood and tissue samples will be labeled with the subject's unique study number and physically stored. During the life of the study, these biospecimens remain available only to the study team and only those exploratory analyses listed in Table 7 will be considered, unless added through a protocol amendment. For analyses that require research collaborations outside of UF, only de-identified specimens will be shared. Samples will be stored for the life of the study and will then be destroyed or transferred to a UF CTSI Biospecimen bank for general research use if subjects agree to enroll in the separate banking study.

At study enrollment, all subjects will be given the option to provide permission for their blood and tumor tissue samples to be collected and stored for long-term use (i.e., beyond the life of this study). Thus, future research on remaining biospecimens after the study-specific analyses have been completed can only be considered by subjects providing their additional consent on

an IRB- approved study consent form for optional biobanking. Future specific use of those biomaterials will require secondary IRB approval. At the closure of this treatment trial, any biospecimens remaining from subjects who have provided consent for long-term storage/use will be destroyed or transferred to the UF CTSI Biobank. For subjects who consent to the treatment study, but decline secondary long-term storage, their biomaterials will be destroyed at the completion of the treatment trial and will not be transferred.

Subjects may be given the option to undergo a tumor biopsy at the end of their participation as well.

10. STUDY DRUG INFORMATION

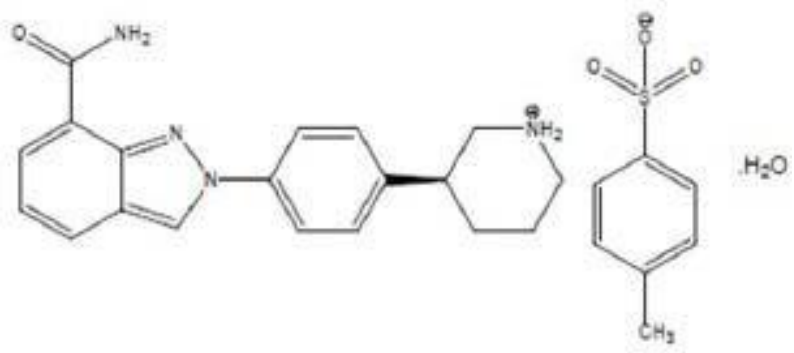
Study Drug Name:

Niraparib (formerly known as MK-4827, TESARO, Inc.)

Identification:

Chemical Name: [3S]-3- [4-31 phenyl] piperidine [tosylate monohydrate salt].

Chemical Structure:



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

Molecular Weight: 510.617 Daltons

Physical Description:

Niraparib drug substance is a crystalline tosylate monohydrate salt. This salt form is non-hydroscopic and is off-white to pale brown in color. Niraparib has an aqueous solubility of 0.80 mg/mL.

10.1 Administration

Niraparib (100 mg) tablets will be administered orally QD continuously. Niraparib will be administered as a flat-fixed dose (100 mg, 200 mg or 300 mg daily), and not by body weight or body surface area. Niraparib should be swallowed whole without chewing. Food does not

significantly affect the absorption of niraparib; therefore, niraparib may be taken without regard to meals. Subjects should take doses at approximately the same times each day. Bedtime administration may be a potential method for managing nausea.

Niraparib treatment should be continued until disease progression.

If a subject misses a dose of niraparib, they should take their next dose at its regularly scheduled time.

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

10.2 Packaging

Packaging: Niraparib drug product is packaged in high-density polyethylene (HDPE) bottles with child-resistant plastic closures. The label test of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries.

All study treatment supplies must be stored in accordance with the storage and handling manual instructions and package labeling. Until dispensed to subjects, the study treatment will be stored in a securely locked area, accessible to authorized staff only.

10.3 Drug Supply

The University of Florida will distribute study drug to affiliate site(s). The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed).

Subsequent study drug shipments will be made after site request for resupply.

10.4 Storage, Handling and Dispensing

All investigational study drug supplies must be store at room temperature and in accordance with the Sponsor's instructions. Refer to the storage and handling manual for further details.

10.5 Contraindications

Treatment with niraparib is contraindicated in individuals with hypersensitivity to any component of the drug, or as indicated within the study protocol.
Subjects and their partners must be completely informed of the risks of pregnancy. Niraparib

may have adverse effects on a fetus in utero. Furthermore, it is not known if niraparib has transient adverse effects on the composition of sperm.

Subjects may not receive niraparib in the study if they are pregnant, planning to become pregnant, or nursing a child. Subjects must agree to use contraception for the entire course of the study and must inform the investigator immediately if they or their partner become pregnant. If a pregnancy occurs, treatment with niraparib will be stopped immediately and the subject will be followed until the end of pregnancy.

10.6 Clinically Reported Adverse Reactions

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

The following adverse reactions and laboratory abnormalities have been identified in ≥10 to 20% of the 367 subjects 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 subjects receiving niraparib: tachycardia, dry mouth, mucosal inflammation, white blood cell count decreased, aspartate aminotransferase increased, alanine aminotransferase increased, and photosensitivity reaction.

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Pre-existing hypertension should be adequately controlled before starting niraparib treatment. Blood pressure and heart rate should be monitored at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with niraparib. Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the niraparib dose, if necessary. In the clinical program, blood pressure measurements were obtained on Day 1 of each 28 day cycle while the patient remained on niraparib. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without niraparib dose adjustment. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Posterior Reversible Encephalopathy Syndrome (PRES): There have been rare reports of niraparib-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES). PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental

status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinitiating niraparib therapy in patients previously experiencing PRES is not known.

11. ADVERSE EVENTS

11.1 Definition

The term "adverse event" (AE) includes any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the wellbeing of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically significant (e.g., that requires unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study). An AE is therefore any unfavorable and unintended symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.
The adverse event may be:

- A new illness/condition;
- Worsening of a sign or symptom of a concomitant illness/condition;
- An effect of the study drug; or
- A combination of 2 or more of these factors.

No causal relationship with the study drug or with the clinical study itself is implied by the use of the term "adverse event."

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. AEs will be recorded in the subject CRF. AEs will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition(s) for which the surgery is required may be an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events.

When a clear diagnosis is available that explains the abnormal objective findings, this diagnosis will be recorded as an adverse event and not the abnormal objective findings (e.g., viral hepatitis will be recorded as the adverse event and not the transaminase elevation). If a definitive diagnosis is not available, then the sign(s) (e.g., clinically significant elevation of transaminase

levels) or symptom(s) (e.g., abdominal pain) will be recorded as the adverse event.

Adverse events fall into the categories “serious” and “non-serious.”

11.1.1 Serious Adverse Event

A serious adverse event is one that at any dose of the study drug or at any time during the period of observation:

- Results in death, unless the death is due to expected disease progression as outlined in section 11.2
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. “Medically important” should be marked only if no other serious criteria are met.

An “unexpected SAE” is any SAE for which the nature, specificity or severity is not consistent with the currently known adverse event profile of the investigational agent(s).

NOTE: The following hospitalizations are not considered SAEs in UFHCC clinical studies:

A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event):

- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.

- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

11.1.2 Clarification of the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). Any grade ≥ 3 adverse events per CTCAE is generally considered severe AE. This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.1.3 Non-Serious Adverse Event

A non-serious adverse event is any adverse event not meeting any of the serious adverse event criteria.

11.1.4 Period of Observation

Following the subject's written consent to participate in the study, all SAEs and AESIs must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs and AESIs must continue for 90 days after the last administration of the investigational product (or to a minimum of 30 days post-treatment if the subject starts alternate anticancer therapy). If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., an optional follow-up tumor biopsy). The investigator should notify the DISC of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

The investigator will begin collecting non-serious adverse event (NSAE) information from the time of the subject's written consent and must continue until 30 days after the last administration of the investigational product. This NSAE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. Treated subjects, including those who were prematurely discontinued from the study, will be followed for any adverse events that occur during the study until thirty days following the last dose of study treatment (i.e., the Follow-up Visit). If at any time after the study is completed, an Investigator becomes aware of an SAE that is considered related to the investigational product, the Investigator should report the SAE to the Sponsor's Pharmacovigilance Department within 24 hours of becoming aware of the SAE

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 subject's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.

11.2 Documenting and Reporting of Adverse Events by Investigator

All adverse events must be fully recorded in the subject's case record form.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject 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.

Every attempt should be made to describe the adverse event in terms of a diagnosis that encompasses the component signs and symptoms. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses on the pages of the case report form.

All subjects who have adverse events, whether considered associated with the use of study drug or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Principal Investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

Assessment of Causal Relationship of Study Drug

The Investigator will provide an assessment of the potential causal relationship between adverse events and study medication by determining whether or not there is a reasonable possibility that the event was caused by the study medication. The relationship or association of the adverse event to the study medication will be characterized as not related, probably not related, possibly related, probably related, or related:

- **Not Related**: There is not a temporal relationship to the study drug administration or the adverse event is clearly due only to the progression of the underlying disease state, intercurrent illness, concomitant medication, concurrent therapy or other known cause.
- **Probably Not Related**: There is little or no chance that the study drug administration caused the adverse event; the event is most likely due to another competing cause, including intercurrent illness, progression or expression of the disease state, or a reaction to a concomitant medication or concurrent therapy appearing to explain the reported adverse event.

- **Possibly Related:** The association of the adverse event with the study drug administration is unknown; however, the adverse event is not reasonably attributed to any other condition.
- **Probably Related:** When a reasonable temporal relationship exists between the adverse event and the study drug administration; significant symptoms abate upon discontinuation of the study drug and there is a reasonable explanation based on known characteristics of the study drug and there is no clear association with preexisting disease or therapy, intercurrent illness, concurrent therapy or other factor(s).
- **Related:** When the adverse event is a known side effect of the study drug or there is a temporal relationship to the administration of the study drug; or the adverse event reappears upon re- administration of the study drug (rechallenge); or the significant symptoms of the adverse event abate upon discontinuation of the study drug (dechallenge).

NOTE: For causal relationships needing to be reported to external entities which require a Related/Not Related or Yes/No data format, the categorization of study drug attribution will be as follows:

- Yes, or Related = Related, Probably Related, and Possibly Related
- No, or Not Related = Not Related and Probably Not Related

11.2.1 Intensity of Adverse Events

The intensity of adverse changes in physical signs or symptoms will be graded according to the CTCAE version 4.03. For all other adverse events not described in the CTCAE, the intensity will be assessed by the Investigator using the following categories:

- **Mild (Grade 1)** – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- **Moderate (Grade 2)** – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
- **Severe (Grade 3)** – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible.
- **Life-threatening (Grade 4)** – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.
- **Death (Grade 5)** – the event resulted in death.

11.2.2 Action Taken with Study Drug

The action the Investigator took with study drug as a result of the event should be recorded as one of the following:

- **None** – No action was taken with regard to the study drug as a result of the adverse event.
- **Interrupted** – Study drug was stopped due to the adverse event, but was later resumed at the same dose.
- **Dose decreased** – The dose of study drug was decreased as a result of the adverse event.
- **Permanently discontinued** – The subject was withdrawn from the study due to the adverse event.

Only one item should be chosen. If multiple actions apply, the following "worst case" scenario hierarchy should be used to determine the preferred entry:
Discontinued > dose decreased > therapy interrupted.

11.2.3 Definition of Outcome

The outcome of the AE should be recorded as one of the following:

- Resolved without sequelae – The subject fully recovered from the adverse event with no observable residual effects.
- Resolved with sequelae – The subject recovered from the adverse event with observable residual effects.
- Not resolved – The adverse event was present at the time of last observation.
- Death – The subject died as a result of the adverse event.

11.3 Immediately Reportable Events

11.3.1 Serious Adverse Events

Serious adverse events (SAE's) and adverse events of special interest (AESIs) must be emailed to the UFHCC DISC Safety Team within 5 days of discovery of the event and the UFHCC Project Management Office (pmo@cancer.ufl.edu) within 24 hours of discovery of the event. The original copies of any reports and related email correspondence must be kept within the study files at the study site. The site investigator is responsible for informing the UF IRB and/or the Regulatory Authority of the SAE as per local requirements.

Follow-up information will be emailed or faxed to the UFHCC Project Management Office (pmo@cancer.ufl.edu), stating that this is a follow-up to the previously reported SAE and giving

the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated\, and whether the participant continued or withdrew from study participation

Institution SAE and Pregnancy Reporting Information
SAE reports must be emailed to the DISC Coordinator, or assigned designee, and the UFHCC Project Management Office at: Email: UFHCC-DSMB@ahc.ufl.edu and pmo@cancer.ufl.edu

11.3.2 Other Events Requiring Immediate Reporting

All pregnancies, regardless of outcome, must be reported to the UFHCC DISC, including pregnancies that occur in the female partner of a male study subject. All pregnancies must be followed to outcome even if the subject was withdrawn from the clinical study or the clinical study was completed. TESARO/GSK will be informed of all pregnancy outcomes as the event is made aware to the UF Health Cancer Center. Any pregnancies of female study subjects and partners of male study subjects that occur within 180 days following the last dose of study treatment must be reported.

The Coordinating Center has the responsibility to monitor the outcome of all pregnancies reported during the Investigator Sponsored Trial. The Coordinating Center must report all pregnancies associated with TESARO/GSK product including follow up outcomes to TESARO/GSK within 24 hours of awareness.

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

An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy on the Pregnancy Outcome Report Form.

Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form, reported as an SAE (e.g., maternal serious complications, therapeutic abortion, ectopic

pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Coordinating Center and TESARO/GSK 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 subject harm while the study treatment is in the control of the health care professionals or subjects. 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 subject, at a dose greater than that which was assigned to that subject per the study protocol and under the direction of the Investigator. If an overdose with a TESARO/GSK product, the Coordinating Center and TESARO/GSK should be notified immediately, and the subject 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 subject because of the overdose, should be reported.
- **Accidental /Occupational exposure**: is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong subject).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure associated with a TESARO/GSK product must be reported on a Special Situations Report Form to the Coordinating Center and to TESARO/GSK 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 Coordinating Center and to TESARO/GSK within 24 hours of awareness.

Although overdose (dose variance of >33%) and cancer are not always serious by regulatory definition, these events should also be reported to the DISC in an expedited manner. In case the

overdose did not result in any adverse event, the Investigator should report this as “overdose, no adverse event” on the SAE form and provide the intended amount, as well as the actual amount, of drug administered. In the event of overdose or exaggerated response, appropriate supportive measures should be employed. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

Overdoses should be documented and reported per the SAE reporting guidelines in section above.

11.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

For any AE that is serious, associated with the use of the study treatment, and unexpected (defined as any term not listed in the expectedness section of the current Investigator’s Brochure or current prescribing information) additional reporting requirements are described below. These types of reports are referred to as (SUSARs).

For interventional clinical trials, if the SUSAR is fatal or life-threatening, associated with the use of the study treatment, and unexpected, the Sponsor will report to Regulatory Authorities and Independent Ethics Committees (IECs) within 7 calendar days after the Investigator learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).

For all other SUSARs, the Sponsor will report to Regulatory Authorities and IECs within 15 calendar days after the Sponsor learns of the event.

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

11.4.1 SUSAR Distribution

A central contact at the Coordinating Center is responsible for the review and distribution of any SUSARs received from TESARO/GSK for TESARO/GSK’s Investigational Product for the duration of this study.

Adverse Events of Special Interest

Selected nonserious AEs and SAEs are also known as Adverse Events of Special Interest (AESI) and must be reported within 24 hours of awareness of the event to the Coordinating Center and to TESARO/GSK regardless of causality assessment to study drug.

11.4.2 Adverse Events of Special Interest (AESI)s

Adverse Events of Special Interest (AESI)s for this trial are defined as:

- 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 Coordinating Center and to TESARO/GSK upon awareness for any subject who has received niraparib (regardless of the timeframe since the last dose).
- Pneumonitis should be reported to the Coordinating Center 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.

For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization criteria) and other sample testing reports related to MDS/AML. The site must keep a copy of the report with the subject's study file.

11.4.3 Sponsor Reporting

Sponsor will forward any SAE, AESI, or pregnancy to GSK within 24 hours of becoming aware of the event. The institution will forward both initial and follow-up versions of each report.

The Sponsor must provide a causality assessment and must sign and date any SAE reports.

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

GSKSAE, AESI, and Pregnancy Reporting Information
OAX37649@GSK.com

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

11.4.4 Reporting Product Quality Complaints for Niraparib

Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the sponsor-investigator or qualified designee to TESARO (tesaro.qa@gsk.com) within 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 (1-844-4TESARO). The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

11.4.5 IND Safety Reports Unrelated to this Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

12.0 STATISTICAL METHODS

The sections below provide an overview of the statistical considerations and analyses.

12.1 Sample Size Determination

Cohort A: Simon's optimal two-stage design will be used for Cohort A. The null hypothesis that the true objective response rate (ORR) is 10%. This is based upon prior evidence that the vast majority of tumors without DNA repair deficiencies are unaffected by the use of PARP inhibition. The null hypothesis will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 2 or fewer responses in these 18 patients, the study will be stopped. Otherwise, 17 additional patients will be accrued for a total of 35. The null hypothesis will be rejected if >= 7 responses are observed in 35 patients. This design yields a type I error rate of 0.05 and power of 90% when the true ORR is 30%.

Cohort B: The sample size for Cohort B is based on an estimated increase in the ORR from 10% (H0) to 50% (H1) in this molecularly selected/enriched patient population. A sample size of 9 patients achieves at least 90% power to detect a difference of 40%, using a one-sided exact test with a significance level of 0.05. Considering 20% dropout rate, we will accrual a total of 12

patients for Cohort B.

Thus, a total sample size of 47 subjects is proposed inclusive of both Cohorts A and B.

Optional Cohort A Expansion: Given the histologic heterogeneity of subjects in Cohort A (all serving as means to enrich for BAP1 mutations), so as not to miss a legitimate signal of activity in a histology-specific manner, we will consider an optional cohort A expansion of any histology that suggests substantial activity. Thus, after completion and analysis of the primary endpoint in Cohort A, and independent of the final ORR for the entire cohort, if the ORR is >30% (H1) within any of the histology categories required for eligibility (i.e., mesothelioma), an expansion cohort of an additional 20 subjects of that specific histology will be considered, pending further discussion with the study team and procurement of funding. This can be performed for each of the four histologies defined in Cohort A, and about 20 to 80 additional subjects may be enrolled to up to four histology-specific expansion groups. This histology-specific expansion (20 minimum) provides > 80% power to assure a degree of activity (one-sided alpha 0.05; Beta 0.10; ORR 10% (H0) to 30% (H1)) suggested by the initial Cohort A analysis.

12.2 Analysis of Primary Endpoint

Objective response rate (ORR as determined by RECIST Version 1.1 criteria) of niraparib treated subjects in each cohort. The ORR is equal to the proportion of subjects achieving a best overall response of partial or complete response (CR + PR), according to RECIST from the start of the treatment until disease progression/recurrence or 30 days after the end of treatment, whichever occurs first. Clinical benefit rate is equal to the objective RR plus the proportion of subjects attaining stable disease (CR + PR + SD). The number of subjects achieving a response will be divided by the total of subjects treated to yield the proportion responding. Exact confidence bounds (95% CI) will be calculated. The primary statistical analysis will use the modified Intention-to-Treat (mITT) population consisting of subjects who are enrolled and received any dose of study medication. The mITT population will be included in summary tables of subject demographics and disease characteristics, and in analysis of efficacy. Statistical analyses will be conducted by the study biostatistician using SAS v9.1 (SAS Institute, Cary, NC).

12.3 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed in a descriptive manner. The PFS rate at 3 and 6 months will be estimated by the Kaplan-Meier (KM) analysis along with median OS based on cohort assignment as well as molecular or histology category. The PFS is defined as the duration of time from study entry to time of progression or death or the date of last contact, whichever occurs first. OS is defined as the time from study entry to time of death or date of last contact. Subjects who did not progress (death) or are lost to follow-up will be censored at the day of their last objective tumor assessment.

12.4 Analysis of Exploratory Endpoints

Exploratory biomarkers will be analyzed post-hoc. Correlative analyses of response and outcomes relative to confirmation/mechanism of BAP1 loss, other DDR pathway dysfunction, histology and homologous recombination deficiency (HRD) status will be performed. HRD assay may be performed in conjunction with third parties to assess predictive response toniraparib treatment. Other analyses will be performed by investigators at the University of Florida. Descriptive statistics and any associated relationships with clinical outcomes will be reported.

12.5 Analysis of Safety Data

The incidence, severity and reversibility of toxicities in subjects treated with niraparib will be performed on all subjects who receive any dose of study medication. Non-serious adverse events that occur more than 30 days after the administration of the last dose of treatment will not be included. The safety and tolerability of treatment is determined by reported AEs, physical examinations, laboratory tests, and ECGs. AEs will be summarized with the incidence and percentage of subjects with at least one occurrence of a preferred term (according to the most severe NCI-CTCAE Version 4.03 grade) will be included. The number of AEs reported will also be summarized. Causality (relationship to study drug) will be summarized separately. Duration of AE will be determined and included in listings along with action taken and outcome.

Laboratory results will be classified according to NCI-CTCAE, Version 4.03. Incidence of laboratory abnormalities will be summarized; laboratory results not corresponding to an NCI- CTCAE Version 4.03 term will not be graded. Laboratory toxicity shifts from baseline to worst grade will also be provided. The results from physical examination and vital sign measurement will be tabulated. Descriptive statistics will be provided as appropriate.

12.6 Interim Analysis

The interim analysis will correspond directly with the Simon two-stage design, as described for Cohort A, in section 12.1. An analysis will be performed after the first 18 subjects are enrolled. At this time the safety and tolerability of the study drug will be assessed and, if deemed safe, enrollment will continue to 35 subjects if three or more subjects demonstrate an objective response.

13. DATA AND SAFETY MONITORING

13.1 Data Integrity and Safety Committee

This protocol will be reviewed and monitored by the University of Florida Health Cancer Center (UFHCC) DISC in accordance with their policies and procedures. They will review and monitor

study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician and study team members. Should any major concerns arise; the DISC will offer recommendations regarding whether or not to suspend the trial.

UFHCC DISC data and safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the sponsor-investigator of recommended action
- Notification of sites coordinated by the UFHCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

In compliance with the UFHCC data and safety monitoring plan, the PI will provide a Data Integrity and Safety Committee Report to DISC at the predetermined timelines for the level of risk category assigned during the initial SRMC review.

UFHCC investigator-initiated protocols will be classified into one of the following categories of risk:

- **Level 1** – Low risk non-therapeutic interventional trials.
- **Level 2** – Moderate risk therapeutic (i.e., drug, biologic, or device) trials using FDA approved or commercially available compounds or interventions.
- **Level 3** – High risk therapeutic trials (i.e., investigator-sponsored INDs, Phase I trials, studies requiring biosafety approval, or other areas that may be designated by NIH as high risk).
- **Level 4** – Complex trials involving very high risk to subjects and a high level complexity (i.e., first in human or gene transfer studies).

The PI will summarize and provide DISC with all pertinent data related to the level of risk assigned by SRMC.

This protocol summary will include a minimum of the following:

- The UF IRB assigned protocol number, UFHCC assigned protocol number, protocol title, PI name, data coordinator name or primary study coordinator, regulatory coordinator name, and statistician
- Date of initial UF IRB approval, date of most recent consent UF IRB approval/revision, date of UF IRB expiration, study status, and phase of the study, Study target accrual and study actual accrual.
- Protocol objectives with supporting data and list of number of study participants who have met each objective.

- Measures of efficacy.
- Early stopping rules with supporting data and a list of the number of study participants who have met the early stopping rules.
- Summary of toxicities and protocol deviations.
- Summary of any recent literature which may affect the safety or ethics of the trial.

13.2 Site Monitoring

UFHCC monitors will make monitoring visits either remotely or to the trial sites periodically during the trial to ensure that sites are complying with the protocol. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The site investigator/institution guarantee access to source documents by UFHCC or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by any collaborating sponsors or their designee as well as inspection by appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

13.3 Principal Investigator Responsibilities

As part of the responsibilities assumed by conducting this study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol.

The PI will be primarily responsible for monitoring of adverse events, protocol violations, and other immediate protocol issues. The study coordinator will collect information on subjects enrolled through the use of electronic or paper adverse event (AE) forms, CRFs, and Informed Consent forms.

14. EMERGENCY PROCEDURES

14.1 Emergency Contact

In emergency situations, the treating physician should contact the Principal Investigator by telephone at the number listed on the title page of the protocol.

14.2 Emergency Identification of Investigational Products

This is a non-blinded, open label, non-randomized study. Thus, there will be no need for unmasking procedures, and the identification of the investigational product can be made by simple inquiry to the investigational pharmacy.

14.3 Emergency Treatment

During and following a subject's participation in the study, the treating physician and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study.

15. ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

15.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Principal Investigator and Co-Investigators abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive UF Institutional Review Board (IRB) approval before initiation of the study.

The Principal Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

All potential serious breaches must be reported immediately to the UFHCC DISC and UF IRB of record, if applicable. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

15.2 Institutional Review Board

Before study initiation, the investigator must have written and dated approval from the UF IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the UF IRB with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the UF IRB with reports, updates, and other information (e.g., amendments, and administrative letters) according to

regulatory requirements or institution procedures.

15.3 Compliance with Laws and Regulations

It is intended that the proposed study be conducted according to the International Conference on Harmonization E6 Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki. Please refer to the International Conference on Harmonization and GCP: http://www.fda.gov/oc/gcp/guidance.html; Declaration of Helsinki: http://www.fda.gov/oc/health/helsinki89.html; Code of Federal Regulations, Title 21: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm

All UF Health Cancer Center investigator-initiated trials, meeting the criteria of the FDAAA's applicable clinical trials, will be registered with ClinicalTrials.gov by the Protocol Development Officer or assigned designee. All studies must be registered no later than 21 days after enrollment of the first participant. The Protocol Development Officer will maintain the responsibility of updating trials registered with ClinicalTrials.gov; per the FDA's updating requirements of information must be updated at least every twelve months and the registry must be updated within thirty days of any changes in recruitment status or completion of the study.

15.4 Delegation of Investigator Responsibilities

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions. The Principal Investigator will maintain a list of Co-Investigators and other appropriately qualified persons to whom he has delegated significant study-related duties.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

15.5 Subject Information and Informed Consent

Before being enrolled in this clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all ICH, GCP, and locally required regulatory elements. The document must be in a language understandable to the subject and must specify the person who obtained informed consent.

After reading the informed consent document, the subject must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The subject's consent must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the subject.

The PI will retain the original signed consent document. The PI will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

15.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Subjects will be told that the UF IRB, UF Health DISC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law.

15.7 Protocol Amendments

Once the study has started, amendments should be made only in exceptional cases. Protocol amendments cannot be implemented without prior written UF IRB approval except as necessary to eliminate immediate safety hazards to subjects. A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the UF IRB and CRO are notified within five business days. All amendments will be submitted to the UF IRB and written verification that the amendment was submitted and subsequently approved is to be obtained.

15.8 Case Report Forms

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account.

An electronic case report form (eCRF) is required and must be completed for each included

subject. The completed dataset is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC.

15.9 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, UF IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

UF Health Cancer Center requires that all study documentation be maintained for at least 6 years from the date of final study publication. No study records may be destroyed without prior authorization from UF.

15.10 Sub-Site Management and Communication Plan

On a weekly basis for the duration that the site has subjects on study treatment, the UFHCC Project Management Office will be in communication with each sub-site to receive updates on study and subject status. Communication will be in the form of e-mail, phone, and weekly study meetings that include at least one representative from each site. Adverse events and regulatory status approvals / updates will be standing agenda items at these meetings. Once all site subjects are completed with the treatment phase of the study (i.e., in the follow up phase, withdrawn, or deceased), meeting frequency may be decreased.

De-identified site data, as well as site study team records, will be reviewed (at a minimum) approximately at least every 12-16 weeks to ensure accuracy and up-to-date certifications / local approvals are on file. All local approval documentation by IRB or otherwise must be provided to UFHCC and contained in the site's regulatory files.

Protocol amendments with red-lined, clean versions and a summary of changes will be provided to sites for IRB submission. Consent form (ICF) amendments will be provided in the study's model consent and will contain tracked changes. Updates to the local ICF must be approved by UFHCC PMO prior to submission to the local IRB. Other document updates such as to the Investigator Brochure and lab manual must be submitted to the local IRB as per their guidelines.

Activated secondary sites are expected to submit modifications to their local IRBs, per local guidelines within 4 weeks of receipt unless otherwise noted. All approval documentation must be forwarded to UFHCC PMO within 2 weeks of approval. If the IRB of record for a sub-site is UF-IRB-01, UFHCC PMO will submit updates on the site's behalf with input from the sub-site(s). Approval will be provided via email to the sub-site(s) as soon as possible when obtained. The University of Florida IRB requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined.

Documentation of participating site's IRB approval of annual continuing reviews, protocol amendments, SAE reports, and protocol deviations, regulatory violations and unanticipated events must be kept on file at UFHCC PMO.

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17. APPENDICES

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Appendix A: SCHEDULE OF EVENTS

Visit:	SCREENING	BASELINE	ON-TREATMENT		EOT	FOLLOW-UP
Procedure:	**(Day -21 to Day 0)**	**(Cycle 1/Day 1/pre-dose)[3]**	**(Cycle 1 /Day 15 ± 1 day)**	**(Cycle 2 & after/ Day 1)**	**(Within 7 days of last study drug administration)**	**(30 +/- 3 days Post EOT)**
Informed Consent	X					
Medical History	X					
Toxicity Assessment	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X
Height	X	X	X	X	X	X
Weight	X	X	X	X	X	X
Vital Signs11	X	X	X	X	X	X
ECOG PS	X	X	X	X	X	X
CMP	X	X	X	X	X	X
Pregnancy Test (Urine or serum)	X	X		X		
CBC w/Diff	X	X[4]	X[4]	X	X	X
Research Blood collection		X	X	X	X	X
Diagnostic Imaging Scan/TA[1]	X[2]			X[6]	X	
Tumor Biopsy	X[7]				X[7]	
Administration of Niraparib		X[5]	X[5]	X[5]		
Concomitant Medication Review	X	X	X	X	X	X
Adverse Event Review		X	X	X	X	X[10]
Survival assessment						X[8]
Follow-up for MDS/AML						X

Bone marrow aspirate and biopsy and sample collection (whole blood) for cytogenetic analysis		x[9]

Abbreviations: PS=ECOG performance status; VS=vital signs (blood pressure, temperature, pulse and respiratory rates, weight and height); CBC/diff=complete blood count and white blood cell differential; CMP=12 item complete metabolic profile (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, AST, ALT, total bilirubin, uric acid)

1) TA= Tumor assessment by RECIST. Diagnostic CT scan, ultrasound, PET/CT scan and/or MRI scan.
2) The radiographic assessment must be repeated if there are more than 28 days between baseline and day 1.
3) Baseline studies must be repeated on day 1 if there are more than 14 days between baseline and day 1.
4) CBCs are to be collected weekly for Cycle 1. For Cycle 1, obtain CBC on Days 1, 8, 15, and 22.
5) Niraparib to be taken daily during each cycle.
6) Imaging scan to be obtained every 8 weeks (+/- 7 days) from first dose (Cycle 1 Day 1) until disease progression or death
7) FFPE from pre-existing tumor specimen (from a routine biopsy) is required to be submitted at study enrollment. See Section 9.3. Tumor biopsy upon disease progression is optional, but recommended. Visit window for EOT visit does not apply for this procedure, as this may be done beyond 7 days past last study drug administration.
8) Overall survival to be followed
9) For any subject diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria) and other sample testing results related to MDS/AML.
10) Collection of all SAEs and AESIs must continue for 90 days after the last administration of the investigational product (or to a minimum of 30 days post-treatment if the subject starts alternate anticancer therapy).
11) Blood pressure and heart rate should be monitored at least weekly for the first 2 months, and then monthly for the first year and periodically thereafter during treatment with niraparib. Participants may take readings at home or locally to them and a site visit is not necessarily required.

Appendix B: ECOG PERFORMANCE STATUS SCALE

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

Appendix C: RECIST GUIDELINES (VERSION 1.1)

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or non-measurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Non-measurable

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

Special Considerations for Lesion Measurability

Bone Lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft t issue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.

- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor non- measurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If non-cystic lesions are presented in the same subjects, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements.

Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the CRF in millimeters (or decimal fractions of centimeters [cm]).

Non-target Lesions

All other lesions (or sites of disease) are identified as non-target lesions (chosen based on the representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and are not recorded or followed.

Specifications by Methods of Measurement

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given subject. If prior to enrollment it is known a subject is not able to undergo CT scans with intravenous contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without intravenous contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will be considered measurable only when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

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

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete response (CR).

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if\ the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

PET Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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.

Not Evaluable (NE): When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Non-target Lesions

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

Non-CR/ non-PD: Persistence of 1 or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing non-target lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. The best overall response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point.) Table 8 provides a summary of the overall response status calculation at each time point for subjects who have *measurable disease* at baseline.

Table 8- Time Point Response: Subjects with Target or Measurable Disease

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 evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Table 9 is to be used when subjects have *non-measurable* disease only.

Table 9- Time Point Response: Subjects with Non-Target or Non-Measurable Disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluable	No	NE
Unequivocal	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; SD = stable disease.

[a] non-CR/non-PD is preferred over SD for non-target disease due to SD being increasingly used as an endpoint for assessment in trials; to assign this category when no lesions can be measured is not advised.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before subject begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. Normally, all target and non- target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Duration of Response

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

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 (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Appendix D: SUBJECT PILL DIARY

Subject Pill Diary			
Treatment Date	**Time**	**100 mg Niraparib pill**	**Comments**
1			
2			
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Subject's Name_____ Cycle # _____

Subject's Signature: _____

Research Office will complete this section:

1. Complete dates: Start date_____ End Date _____
2. Total number of Niraparib pills to be taken (per protocol)(100 mg): _____
3. Compliance rate_____%
4. Physician/Nurse/Research Staff's signature: _____

18. SUMMARY OF CHANGES

Version	Section(s) Affected	Change History	Date of Changes
2.0	**Throughout protocol**	**The word patient replaced with subject.**	**10-Oct-2019**
	Site Protocol Signature Page	**Signature lines added for local investigators**	
	Study Design	**Updated** **This is a prospective, open-label phase II study in two biologically distinct cohorts.**	
	Inclusion Criteria	***Removed Criteria*** **Must be willing to provide blood/serum/plasma for all aspects of protocol specific research purposes.** ***Updated Criteria*** Must have formalin-fixed paraffin embedded (FFPE) tissue available for research purposes. Tissue must have been obtained within the last 3 years from a core or excisional biopsy. **A medical history with prior exposure to standard systemic therapy (having exhausted or declined all known and currently approved effective life prolonging therapies.**	
	Section 1.6.1	**Information regarding routine safety monitoring of PN001 has been removed.**	
	Section 2.0	***Updated*** **2.1 Primary** To determine the objective response rate (ORR) for subjects with BAP1 and other DDR repair pathway deficiencies treated with niraparib. 2.2 Secondary **To determine the median progression free survival (PFS) and estimate PFS at 3 and 6 months in each cohort and histologic subsets of subjects. PFS is defined as the duration of time from study entry to time of progression or death or the date of last contact, whichever occurs first.**	
	Section 4.1	*Updated* A total of 47 subjects are to be enrolled with thirty-five subjects in Cohort A and twelve subjects in Cohort B. Additionally, there is the possibility of further subject enrollment (a pre-specified optional expansion cohort of up to an additional 20 subjects [to obtain 18 evaluable]) based on meeting a minimum ORR in each specific histology identified in Cohort A (See Section 12.1).	
	Section 5.0	*Updated* All consented subjects must be entered into the University of Florida's Clinical Trial Management System (OnCore) prior to assignment of a subject identification number. This is not registration into the trial. The study team must submit the	

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		completed study specific eligibility checklist, supporting source documentation and a copy of the signed informed consent document(s) to the UFHCC Project Management Office (PMO; PMO@cancer.ufl.edu) or their assigned Project Manager. Unsigned eligibility checklists or eligibility packets with missing or incomplete information may be returned to the study team. Upon receipt of a completed eligibility packet, the designated Project Manager will review the source to verify eligibility and assign a subject number. If eligibility cannot be confirmed, the project manager will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be able to participate in the trial.	
	Section 6.1	***Updated*** CT or PET/CT scans, or MRI scans of the chest, abdomen, and pelvis will be obtained for tumor measurement (NOTE: baseline study imaging must be performed within 28 days prior to initiation of study therapy). Imaging studies used at study entry to establish baseline tumor measurement(s) should be the imaging modalities used to monitor subsequent disease response.	
	Section 6.5	***Updated*** A tumor biopsy will be done upon progression of disease (with subject's permission) for research purposes. The timing of the research biopsy should be ideally within 7 days of the EOT visit or at least prior to the start of any subsequent anticancer therapy. ***Added*** **If feasible, the EOT visit, except for the biopsy noted in 6.5, should be performed within seven days regardless of the reason for discontinuation. If the subject withdraws consent, however, no further study procedures can proceed."**	
	Section 6.6	**+/- 3 days window has been added** ***Added*** **Follow-up Evaluations should occur regardless of the reason for discontinuation. If the subject withdraws consent, however, no further study procedures can proceed** ***Updated*** **Subjects will additionally be followed every three months for vital statistics and development of MDS/AML until death.**	
	Section 7.1	**Updated** ***For subjects whose starting dose is 2 capsules once daily, escalation to 3 capsules once daily is required at the discretion of the treating provider at the beginning of cycle 3, if no treatment interruption or discontinuation was required during the first 2 cycles of therapy, and the treating physician**	

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		documents no other justification to maintain the lower dose."	
	Table 3	Niraparib dosing has been updated	
	Section 7.3	***Added*** **If initial starting dose was 200 mg/day but subsequently increased to 300 mg/day at cycle 2, dose reductions are to follow as if they started at 300 mg/day."**	
	Section 7.3.1	*Updated* Withhold niraparib for a maximum of 28 days or until adverse reaction has improved to < Grade 1. Resume niraparib at a one dose level reduction per Table 4."	
	Section 7.3.2	***Added*** ***** Discontinue niraparib if the platelet count, neutrophils and/or hemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the subject has already undergone dose reduction to 100 mg once daily.*****	
	Section 8.3	***Updated*** **Subjects who do not receive any doses of study drug will be replaced. Subjects who receive any dose of study drug will contribute to safety and toxicity data, but will be replaced if they cannot provide response assessment due to study discontinuation for reasons other than disease progression or toxicity."**	
	Section 9.1	***Added*** **Discussion with the PI prior to biopsy is recommended.**	
	Section 11.1.1	***Updated*** Results in death, unless the death is due to expected disease progression as outlined in section 11.2.	
	Section 11.4.4	**Fax number has been changed to +1-866-750-6823**	
	Section 12.1	***Updated*** **A sample size of 9 patients achieves at least 90% power to detect a difference of 40%"**	
	Section 12.2	***Removed*** **Subjects who do not have a tumor response assessment for any reason will be considered nonresponders and will be included in the denominator when calculating the response rate.**	
	Section 12.3	***Added*** **The PFS is defined as the duration of time from study entry to time of progression or death or the date of last contact, whichever occurs first. OS is defined as the time from study entry to time of death or date of last contact.** ***Updated*** **Subjects who did not progress (death) or are lost to follow-up**	

Version	Section(s) Affected	Change History	Date of Changes
		will be censored at the day of their last objective tumor assessment.	
	Section 13.2	***Updated*** **UFHCC monitors will make monitoring visits either remotely or to the trial sites periodically during the trial to ensure that sites are complying with the protocol.**	
	Appendix A	***Updated*** 6) Imaging scan to be obtained every 8 weeks until progression. 7) FFPE from pre-existing tumor specimen (from a routine biopsy) is required to be submitted at study enrollment. See Section 9.3. Tumor biopsy upon disease progression is optional, but recommended. Visit window for EOT visit does not apply for this procedure, as this may be done beyond 7 days past last study drug administration. *Removed* **8) Overall survival to be followed for 5 years following the last dose of niraparib.**	
2.1	**Abbreviations**	Added GSK	29-Oct-2020
	Throughout protocol	-Added "urine or serum" for pregnancy test -Updated TESARO to TESARO/GSK -Added +/- 1 day to dosing cycle to be consistent with visit windows -Updated at least 8 weeks to approximately 8 weeks for study participants on the study.	
	Inclusion Criteria in Protocol Synopsis and Section 4.2	Added "oral" in front of corticosteroids	
	Exclusion Criteria in Protocol Synopsis and Section 4.2	Corrected Exclusion Criteria lettering	
	Section 6.4, Appendix A #6	Imaging intervals clarified to be every 8 weeks +/- 7 days from C1D1	
	Section 7.3 (Table 4)	If starting dose is 2 capsules once daily, then escalation to 3 capsules once daily, at the beginning of cycle 3	
	Section 10.6	Added hypertension and PRES language from IB v11.	
	Section 11.4.3	Updated email address and name to current GSK for reportable events	

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	Section 15.10	Added Subsite Management and Communication Plan	
	Appendix A #11	Added footnote #11 about heart rate and blood pressure monitoring.	
2.2	**Title Page**	Added Dr.Franke as Junior PI	14-Feb-2022