Niraparib Plus Carboplatin in Patients with Homologous Recombination Deficient Advanced Solid Tumor Malignancies

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Study Drug: Niraparib capsule
IND Number: 132931
Clinical Phase: Ia/Ib
Number of Subjects: 18-146

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements including but not limited to Institutional Review Board/Ethics Committee (IRB/EC) approval.

Confidentiality Statement

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SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: Niraparib Plus Carboplatin in Patients with Homologous Recombination Deficient Advanced Solid Tumor Malignancies

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

_____ _____

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INVESTIGATOR SIGNATURE PAGE

Declaration of the Investigator

Title: Niraparib Plus Carboplatin in Patients with Homologous Recombination Deficient Advanced Solid Tumor Malignancies

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

_____

Investigator Name: Date
Site Name:

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATM	Ataxia telangiectasia mutated (ATM),
ATR	Ataxia telangiectasia and Rad3 related (ATR)
ATRX	Alpha thalassemia/mental retardation X-linked
AUC	Area under the curve
BAP1	BRCA1-binding protein
BARD1	BRCA1-associated RING domain
BER	Base excision repair
β-hCG	β-human chorionic gonadotropin
BRIP1	BRCA1 interacting protein C-terminal helicase 1
BUN	Blood urea nitrogen
CBC	Complete blood count
CHEK1/CHEK2	Checkpoint kinase 1 and 2
Cis	Cisplatin
CLIA	Clinical laboratory improvement amendments
CNS	Central nervous system
COE	Centers of excellence
CR	Complete response
pCR	Pathologic complete response
CRC	Colorectal cancer
CRF	Case Report Form
CRO	Clinical research organization
CT	Computed tomography
CYP	Cytochrome P450
DCR	Disease control rate
DDR	DNA damage response
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic acid
DSMB	Data and safety monitoring review board
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
FFPE	Formalin-fixed, paraffin embedded
GCP	Good clinical practice
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HR	Hazard ratio
HR	Homologous recombination
HRD	Homologous repair deficiency
ICH	International Conference on Harmonisation
IEC	Independent ethics committees
IHC	Immunohistochemistry
INR	International normalized ratio
IV	Intravenously
LCCC	Lombardi Comprehensive Cancer Center
LD	Longest diameter
LFT	Liver profile
LLN	Lower limit of normal
LMWH	Low molecular weight heparin

LOH	Loss of heterozygosity
LSST	Large scale state transition
MDS	Myelodysplastic syndrome
MRI	Magnetic resonance imaging
MRN	MRE11-RAD50-NBS1
MSI	Microsatellite instability
MSS	Microsatellite stable
MTD	Maximum tolerated dose
MTT	Molecularly-tailored therapy
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NER	Nucleotide excision repair
NGS	Next-Generation Sequencing
NHEJ	Non-homologous end joining
NR	Not Reported
ORR	Objective response rate
OS	Overall survival
PALB2	Partner and localizer of BRCA2
PARP	Poly (ADP-ribose) polymerase
PET	Positron emission tomography
PD	Progressive disease
PDX	Patient-derived xenografts
PFS	Progression-free survival
PGP	P-glycoprotein
PI	Principal investigator
PK	Pharmacokinetics
PO	By mouth
POR	Proof of receipt
PR	Partial response
PS	Performance Status
PT	Paclitaxel
PT	Prothrombin time
PTT	Partial thromboplastin time
RCB	Residual cancer burden
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
RR	Response rate
SAE	Significant adverse event
SD	Stable disease
SRS	Stereotactic radiosurgery
SSB	Single-strand break
SUSAR	Suspected unexpected serious adverse reactions
TAI	Telomeric allelic imbalance
TJU	Thomas Jefferson University
TLS	Translesion synthesis
TNBC	Triple negative breast cancer
ULN	Upper limit of normal
WHO	World Health Organization

STUDY SYNOPSIS

Title	Niraparib Plus Carboplatin in Patients with Homologous Recombination Deficient Advanced Solid Tumor Malignancies
Short Title	Niraparib Plus Carboplatin in HR Deficient Advanced Solid Tumors
Protocol Number	2017-0085 (Georgetown University Parent IRB); (CRC #112016-01)
Clinicaltrials.gov number	NCT03209401
Phase	Phase Ia/Ib
Investigational Agents	1. Niraparib, an oral PARP inhibitor (GSK) 2. Carboplatin
FDA IND number	132931
Indication	Advanced solid tumor malignancies with evidence of homologous recombination deficiency (HRD).
Study Overview	This is a multi-institutional Phase I dose-escalation and dose-expansion trial for patients with advanced, solid tumor malignancies who have pre-identified deleterious germline or somatic mutations in the homologous recombination deoxyribonucleic acid (DNA) repair pathway (HR deficient). The trial is designed to assess the efficacy and safety of niraparib plus carboplatin in patients with evidence of HRD. The primary endpoint will be identifying the recommended phase 2 dose (RP2D) and schedule of niraparib plus carboplatin, as well as establishing the anti-tumor efficacy of niraparib plus carboplatin as determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Patients will be pre-identified from participating centers as having either a germline deleterious mutation or tumor expression of a deleterious mutation in one of the genes listed below, as determined by Next-generation DNA sequencing (NGS) only, completed prior to enrollment in this protocol. Patients with advanced solid tumor malignancies with the presence of somatic or germline deleterious mutation in a gene(s) critical to DNA repair through homologous recombination, including but not limited to: *RAD50/51/51B, BARD1, BLM, BRCA1, BRCA2, BRIP1, FANCA/C/D2/E/F/G/L, PALB2, or BAP1,* and who have an adequate performance status (PS), bone marrow, hepatic, and renal function as well as biopsiable and measurable disease will be screened for enrollment. Appropriate patients will be enrolled in a 3+3 alternating dose escalating fashion, to a maximum dose of niraparib of 300mg daily and a maximum dose of carboplatin area under the curve (AUC) of 4. The 3+3 schema will be employed to ensure safety and tolerability. Once the RP2D and schedule are identified, a Phase Ib expansion cohort of 20 additional patients will be enrolled as a pilot subgroup to determine efficacy. Of the 20 patients in this Phase Ib cohort, no more than 10 patients will have underlying breast cancer; and additionally no more than 10 patients may harbor *BRCA1* or *BRCA2* mutations. To assess the efficacy of poly (ADP-ribose) polymerase (PARP) inhibition and the extent of DNA damage, patients will undergo serial tumor biopsies to measure DNA damage as quantified by levels of γH2AX and RAD51 foci formation, as well as an assessment of PARP inhibitory activity. Tumor biopsies will also be used to assess the mechanisms of resistance to PARP inhibitor-based therapy. Assessment of safety including blood tests, clinic visits and exams will occur weekly at the start of therapy, then will transition to every 3-week clinic visits and

	exams at the beginning of cycle 4. For the Phase Ib portion, patients will undergo weekly lab work and clinic visits for cycle 1 only. We hypothesize that in this HR deficient patient population, the addition of niraparib to carboplatin will lead to significant anti-tumor responses with acceptable toxicities.
Study Duration	48 – 60 months
Study Center(s)	➢ Georgetown University, Lombardi Comprehensive Cancer Center Washington, DC ➢ Additional participating centers to be added upon activation
Objectives	Phase Ia (dose-escalation phase) Primary Objective: To identify the RP2D and schedule of niraparib plus carboplatin for patients with homologous recombination deficient advanced solid tumor malignancies Phase Ib (dose-expansion phase) Primary Objective: To determine the anti-tumor efficacy of niraparib plus carboplatin in a non-disease specific cohort of patients with homologous recombination deficient advanced solid tumor malignancies, as determined by RECIST v1.1 Secondary Objectives: Clinical: a. To evaluate the safety and tolerability of niraparib plus carboplatin b. To determine evidence of any disease specificity with this combination c. To assess the anti-tumor efficacy of combined therapy as determined by RECIST v1.1 d. To assess the anti-tumor efficacy of combined therapy as determined by measurement of overall survival (OS) and progression free survival (PFS) Scientific: a. To assess the effects of niraparib alone, and niraparib plus carboplatin on pharmacodynamic markers of DNA damage and repair, including γH2AX/RAD51 foci formation, and as measured by the PARP trapping assay b. To explore predictive markers of response and/or resistance to therapy in serial tumor biopsy samples
Number of Subjects	A minimum of 18 patients (assuming 6 patients at the lowest dose of the 3 schedules) A maximum of 146 patients (assuming 6 patients in each cohort and each schedule (21 cohorts) PLUS a 20 patient Phase Ib portion) The *anticipated* number of patients will be approximately 80, accounting for dose escalation to the RP2D, utilization of the alternative schedules, and the 20 patient expansion group.
Diagnosis and Main Inclusion and Exclusion Criteria	Key Inclusion Criteria 1) Histologically confirmed advanced solid tumor malignancy that is amenable to biopsy - A patient's biopsied lesion must be at least 1cm in diameter (in at least one dimension) 2) Pre-identified presence of somatic or germline deleterious mutation in a gene(s) critical to DNA repair through homologous recombination, including but not limited to: *RAD50/51/51B, BARD1, BLM, BRCA1, BRCA2, BRIP1, FANCA/C/D2/E/F/G/L, PALB2, or BAP1* 3) Radiographically measurable disease by RECIST v1.1 4) Age ≥ 18 years 5) Life expectancy of more than 3 months 5) Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 6) Signed informed consent form

	7) Adequate hepatic, bone marrow, and renal function as defined below in the body of the protocol Key Exclusion Criteria 1) Prior exposure to PARP inhibitor-based therapy 2) Prior disease progression while receiving platinum chemotherapy; or disease progression within 6 months of any platinum chemotherapy (including adjuvant or neoadjuvant) except for breast cancer where disease progression cannot have occurred within 12 months of the last platinum chemotherapy 3) Active severe infection, or known chronic infection with human immunodeficiency virus (HIV) or hepatitis B virus 4) Cardiovascular disease problems including unstable angina, therapy for life-threatening ventricular arrhythmia, or myocardial infarction, stroke within the last 3 months, or a diagnosis of congestive heart failure 5) Women who are pregnant or breastfeeding 6) Patients with known untreated central nervous system (CNS) metastases 7) Patients with clinical significant neuropathy, grade 2 or greater 8) Patients with history of another active malignancy within the past 2 years, excluding non-melanoma carcinoma of the skin 9) Patients receiving any other investigational agents
Study Design	This study is a single-arm, open-label, multi-institutional Phase I trial with a dose-escalation (Ia) and dose-expansion (Ib) portion evaluating the combination of niraparib plus carboplatin in homologous recombination deficient advanced solid tumor malignancies. Phase Ia Portion The Phase Ia portion of the study will be used to determine the RP2D and schedule for niraparib plus carboplatin. Patients will be evaluated weekly for the first 3 cycles (9 weeks) and then every 3 weeks thereafter on Day 1 of subsequent cycles. Niraparib will be given daily [redacted] out of a 21 day cycle with the dose determined by the patient cohort. Carboplatin at a maximum AUC of 4 will be administered on Day 2 of every cycle sparing cycle 1 (cycle 1 will be Niraparib alone) (Figure 1). A standard 3+3 design will be employed to ensure safety and tolerability, in which patients are enrolled in cohorts of 3 patients each. If there are less than 2 dose-limiting toxicities (DLTs) in the first 3 patients, then 3 additional patients will be enrolled to the current dose level cohort. If there are less than 2 dose-limiting toxicities (DLTs) in these 6 patients, then 3 additional patients will be enrolled in the next dose level (Table 1), and so on. If there are greater than or equal to 2 DLTs in a given 6 patient cohort, then the dose level below will be considered the maximum tolerated dose (MTD) and will be employed as the RP2D and schedule. If dose level 1 is not tolerated, then an alternative schedule will be pursued.

Figure 1: Treatment and Biopsy Schedule: Niraparib ( )

Dose Cohort	Niraparib (mg Daily)	Carboplatin (AUC)
1		
2		
3		
4		
5		
6		
7		
8		
9		

Table 1: Dose Escalation for Carboplatin and Niraparib (Niraparib Dosing)

Alternative Dosing Schedules

Given concerns over the potential for combinatorial toxicity, especially on myelosuppression, two alternative dosing schedules will be considered. The decision to pursue one or both of these alternative schedules will be determined by the PIs and will take into account toxicities observed to date, as well as the pharmacodynamic effects observed on serial tumor biopsies.

Thus, for example, if dose level 1 is too toxic in Schedule #1 (i.e. with 2 or more DLTs), then patients will be enrolled according to Schedule #2. If Schedule #2 remains too toxic, then Schedule #3 will be employed.

However, the investigators will also be reviewing the pharmacodynamic assessments of DNA damage, and will have the opportunity to compare these results to the clinical efficacy. If these pharmacodynamics assessments suggest that an alternative schedule may be more efficacious, or that an alternative schedule merits scientific exploration, then the investigators may choose as a group to pursue one or both of the alternative schedules. Ultimately, the schedule and the dose must be selected by the investigators prior to enrollment of the Phase Ib expansion cohort – as patients in the Phase Ib expansion cohort will be enrolled in only one RP2D and schedule.

In the first alternative schedule, niraparib will only be dosed on of an every 21 day cycle (Figure 2). The dose escalation will be otherwise similar (Table 2). Carboplatin at a maximum AUC of 4 will still be administered on Day 2 of every cycle sparing cycle 1 (cycle 1 will be Niraparib alone).

Figure 2: Treatment and Biopsy Schedule: Niraparib (Days)

Dose Cohort	Niraparib (mg Daily)	Carboplatin (AUC)
1		
2		
3		
4		
5		
6		
7		
8		
9		

Table 2: Dose Escalation of Carboplatin and Niraparib (Niraparib Dosing)

In the second alternative schedule, patients will receive carboplatin AUC 2 weekly for 2 weeks on, 1 week off of every q3week cycle. In addition, the niraparib will only be given for 4 days, each of the first two weeks ( ). The carboplatin will be given on Days 2 and 9 (Figure 3). For this alternative schedule, there will be no dose escalation of the carboplatin – only the niraparib will be dose-escalated (Table 3).

Figure 3: Treatment and Biopsy Schedule: Weekly Carboplatin

Dose Cohort	Niraparib (mg Daily)

1	[redacted]
2	[redacted]
3	[redacted]

Table 3: Dose Escalation – Weekly Carboplatin

Patients will be evaluated, including laboratory testing, weekly until the first restaging analysis. Restaging will occur every 9 weeks. If at first restaging there is no evidence of progressive disease (PD), as determined by RECIST v1.1 criteria, and the patient is tolerating therapy, then patient will continue with study therapy, with clinic visits and lab work on Day 1 only of future cycles, and restaging imaging every 9 weeks. Patients will continue to remain on study as long as there is no evidence of PD (according to RECIST v1.1 criteria) and the therapy is adequately tolerated.

Pharmacodynamic studies will be directed toward an assessment of DNA damage including γH2AX and RAD51 foci formation, as well as an assessment of PARP inhibitory activity, as measured by a PARP-trapping assay. In addition, a portion of all tumor samples will be used in *ex vivo* models (e.g. organoids) for further analysis of mechanism of resistance and to identify combinatorial therapies that can overcome resistance.

Phase Ib Portion

There will be a Phase Ib expansion cohort including 20 patients to further assess the efficacy of niraparib plus carboplatin, using the RP2D and schedule from Phase Ia. Twenty patients with tumors harboring deleterious mutations in the HR repair pathway (similar to Phase Ia), with no more than 10 patients with breast cancer and no more than 10 patients with *BRCA1* or *BRCA2* mutations will be enrolled.

All patients in the Phase Ib portion will be evaluated with clinic visits, physical exams, and blood tests weekly for the first cycle, then on Day 1 of subsequent cycles only, unless clinically indicated sooner. Restaging will occur every 9 weeks. If at first restaging there is no evidence of PD, as determined by RECIST v1.1 criteria, and the patient is tolerating therapy, then patient will continue with study therapy. Patients will continue to remain on study as long as there is no evidence of PD (according to RECIST v1.1 criteria) and the therapy is adequately tolerated.

All patients in the Phase 1b portion will undergo three serial tumor biopsies to assess the pharmacodynamic effects of niraparib, and then niraparib plus carboplatin on DNA repair. An off study/at progression tumor biopsy will also be required. Correlative studies for the serial tumor biopsies will be the same as for the Phase Ia.

Timing and Utilization of Tumor Biopsies

Pre-Treatment Biopsy

Following successful screening and enrollment of patients with an advanced solid tumor malignancy and known deleterious mutations in selected DNA repair genes, a pre-treatment tumor biopsy will be obtained (within 4 weeks of Day 1 of study treatment).

Second & Third Biopsies (For patients in the Phase Ib portion)

The second biopsy will occur on C1D14 (range C1D10-14) in schedule #1 (the timing of the biopsies in the alternative schedules will differ, as outlined in the full protocol), on niraparib therapy alone. The third biopsy will occur on C2D14 (range C2D10-14) on niraparib and carboplatin therapy. ***There can be some flexibility***

with the timing of the biopsies, but it is important that the second and third biopsies take place on a day that the patient received a dose of niraparib.

Biopsy Upon Progression
All patients whose disease has NOT rapidly progressed on trial will undergo a biopsy upon disease progression for ongoing correlative studies. Specifically, patients who meet the following conditions will have a biopsy upon progression:

- The patient experiences a RECIST 1.1 confirmed partial or complete response at any point, and then subsequently experiences disease progression
  Or
- The patient experiences stable disease of ≥27 weeks (to comport with the timing of restaging imaging), and then subsequently experiences disease progression

Tissue Utilization and Prioritization
A rigorous tumor collection algorithm will be instituted for this protocol. Shipping details and addresses are all summarized in Appendix D.

For each biopsy, 5 individual cores will be obtained with an 18-20 gauge needle. The utilization of the cores differs depending upon which biopsy is being obtained. Please refer to Section 4.3.2 and the Lab Manual for details

<u>Initiation of Treatment, Patient Assessment, and Response Assessment</u>
Prior to treatment initiation, all patients will undergo baseline imaging within 4 weeks of initiating therapy and screening for enrollment within 2 weeks of initiating therapy. At the screening evaluation, the patient's performance status will be confirmed, and standard laboratory tests will be obtained. Patients must have measurable, metastatic disease, as per RECIST v1.1 and the index lesions could not have been previously treated with local therapy, such as radiation.

Treatment will be initiated on Cycle 1 Day 1, and patients will be evaluated weekly while on therapy for the first 3 cycles (9 weeks) and then every 3 weeks on Day 1 of subsequent cycles. These "protocol defined visits" will include a history and physical, update of concomitant medications, assessment of treatment toxicities, laboratory evaluations and may or may not coincide with the regular visits that a physician may wish to have with the patient – BUT these will be required visits used for data collection. Laboratory evaluation will continue weekly through the first 3 cycles for the Phase Ia portion of study and then on D1 only of subsequent cycles unless clinically indicated sooner. For the Phase Ib portion of study, laboratory evaluation will continue weekly through the first cycle only and then on D1 only of subsequent cycles unless clinically indicated sooner. Radiologic response will occur every 9 weeks. Following the first response assessment, any patient with stable or responding disease as per RECIST v1.1 may stay on therapy, and will be evaluated every 9 weeks until disease progression, at which point he/she will be removed from the study.

	Longitudinal Outcomes Assessment Subsequent therapies will be administered at the discretion of the treating physician. All patients will be followed until death for assessment of overall survival.
Multi-Institutional Trial Coordination	Georgetown University's LCCC Consortium IIT Office will oversee the multi-institutional coordination. Patient Enrollment Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send an email within 24 hours containing the patient's initials to the local principal investigator (PI), to Dr. Isaacs, and to Georgetown University's LCCC Consortium IIT Office. If a patient is successfully screened, the local research coordinator must send all supporting documentation to Georgetown University's LCCC Consortium IIT Office by secure email to confirm eligibility. Patients should not start therapy until Dr. Isaacs and Georgetown University's LCCC Consortium IIT Office have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment. Data Collection and Management Patient data will be entered into the on-line accessible database. This database is housed at Lombardi-Georgetown, but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session so that they may learn how to enroll data into the data base. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within 10 business days of each patient visit. Conference Calls A monthly conference call will be held between Lombardi-Georgetown and the other sites to review patient enrollment, toxicity, and response assessment. In addition, a separate conference call will be held between OHSU and the other sites to review sample collection, tissue coordination, and tissue analysis. This will include an ongoing review of the success rate of the tumor biopsies, and of the *ex-vivo* tumor samples. Trial Auditing Georgetown University's LCCC Consortium IIT Office will arrange all primary source documents for the patients to be audited. This will include collecting copies of the primary source data for any patients treated at other sites.
Duration of therapy	All drugs will be administered until disease progression or unacceptable toxicity is observed.
Statistical Design, Feasibility, and Trial Duration	This study is a single-arm, open-label, multi-institutional Phase I trial of the combination of niraparib and carboplatin in patients with advanced solid tumor malignancies with deleterious mutation(s) in DNA damage repair genes. The Phase Ia portion of the trial will be conducted in a 3+3 design, enrolling patients in cohorts of 3 patients each to ensure safety and tolerability. If there are less than 2 dose-limiting toxicities (DLTs) in the first 3 patients, then 3 additional patients will be enrolled to the current dose level cohort. If there are less than 2

	dose-limiting toxicities (DLTs) in these 6 patients, then 3 additional patients will be enrolled in the next dose level (Table 1), and so on. If there are greater than or equal to 2 DLTs in a given 6 patient cohort, then the dose level below will be considered the maximum tolerated dose (MTD) and will be employed as the RP2D and schedule. If dose level 1 is not tolerated, then an alternative schedule will be pursued. There will be a Phase Ib expansion cohort including 20 patients to further assess the efficacy of niraparib plus carboplatin, using the RP2D and schedule from Phase Ia. Twenty patients with tumors harboring deleterious mutations in the HR repair pathway (similar to Phase Ia), with no more than 10 patients with breast cancer and no more than 10 patients with *BRCA1* or *BRCA2* mutations will be enrolled. Efficacy for both Phase Ia and Phase Ib will be assessed by radiologic assessment every 9 weeks for objective response. All patients meeting the eligibility criteria and who have signed a consent form, have begun treatment, are not lost to follow-up, and are not taken off study for reasons other than progression or death before 9 weeks will be considered evaluable for the assessment. The primary endpoint for Phase Ia will be the number of grade 3 and 4 toxicities according to the National Cancer Institute Common Toxicity Criteria for Adverse Events Version 5.0 [NCI CTCAE v5.0], and the primary endpoint for Phase Ib will be anti-tumor efficacy of niraparib plus carboplatin by ORR. Secondary endpoints for both portions of study will include PFS and OS, disease control rate, quantification of DNA damage and repair, quantification of PARP inhibition, and exploration of predictive markers of response and/or resistance to therapy in serial tumor biopsy samples. Interim analyses to assess secondary endpoints of OS and PFS will be scheduled to occur at 12 months and 24 months. Between *18 and 126* patients will be enrolled in the Phase Ia portion of the study, depending on whether DLTs occur and dose de-escalation and/or utilization of the alternative schedules is required. Twenty patients will be enrolled in the Phase Ib portion of the study. With 20 evaluable patients in the Phase Ib portion, combined with a minimum of *18 to a maximum of 126 patients enrolled strictly in the Phase Ia portion of the trial, there will be up to 146* patients enrolled. It is anticipated that approximately 80 patients, however, will need to enroll to complete the trial. At an expected accrual rate of 2-3 patients per month (roughly 30 patients per year), the expected accrual duration will be approximately 48 – 60 months. Descriptive statistics will be used to summarize patients' experienced toxicity. Patients' adverse events and toxicities will be tabulated according to their grades and attributions. PFS and OS will be estimated using the Kaplan-Meier method. As a pilot study with a heterogeneous patient population, no meaningful efficacy statistics can be generated, rather an observation of efficacy. ORR by RECIST v1.1 criteria will be estimated with its 95% exact confidence interval, and will be assessed overall and by tumor subtype (breast/gynecologic, gastrointestinal [esophageal, gastric, colorectal, anal], pancreatobiliary, GU, other). The main purpose of Phase Ib is not hypothesis testing but rather observing the efficacy. However, if we observe at least 5 or more out of the 20 patients who obtain a PR, CR or SD at 9 weeks, this would be equivalent to a one-stage Phase II testing of the response rate of 0.1 vs. at least 0.3 at a 0.05 one-sided alpha level. The sample size of 20 patients would give 80% to reject the null hypothesis of the response rate at 0.1. If, in this study, 6, 7 or 8 patients obtain a PR, CR or SD at 9 weeks, then we are 80% confident that the response rate would be within the range of 16.6%-46.6%, 21.2%-51.2%, or 24.8%-56.8%, respectively.

	Number of Centers Because the qualifying mutation rate is expected to be 5-10%, it will be critical to have access to a large pool of potential patients to be able to recruit between 18 and 146 evaluable patients for this trial. Thus, we propose a multi-institutional trial, with centers enrolling gradually following identification of patients with advanced solid tumor malignancies and deleterious DNA repair gene mutations. Georgetown-Lombardi will act as the primary site, and Georgetown University's LCCC Consortium IIT Office will oversee patient enrollment and on study activities at other sites. Georgetown-Lombardi will also be responsible for generation of the case report forms, which can be accessed through an on-line data entry portal (Training for this portal can be done on-line).

1.0 BACKGROUND AND JUSTIFICATION

1.1 Deoxyribonucleic acid (DNA) Repair

Each of the more than 70 trillion cells in the human body endures tens of thousands of DNA lesions per day[1]. Upon DNA damage, a complex DNA damage response (DDR) pathway is initiated. This includes cell-cycle arrest, transcriptional and post-transcriptional activation of a subset of genes including those associated with DNA repair, and sometimes programmed cell death. If not repaired or repaired incorrectly, DNA lesions can lead to wider scale DNA aberrations, resulting in genomic instability, which is widely accepted as the fundamental etiology of cancer.

DNA lesions are a result of both endogenous and exogenous. Oxidative stress and production reactive oxygen species are a major endogenous source of DNA damage, as well as lipid peroxidation, hydrolytic reactions, and non-enzymatic methylations which generate thousands of DNA-base lesions per cell per day. DNA damage can result from exogenous causes including UV light, ionizing radiation, tobacco-containing products, and environmental/occupational exposures. Reactive oxygen and nitrogen compounds can lead to adducts that impair base-pairing, block DNA replication and transcription, and result in base loss or DNA single-strand breaks (SSBs). DNA double stranded breaks are often formed by exogenous sources of DNA damage, specifically ionizing radiation. Additionally, DSBs can be formed under mechanical stress, when two SSBs arise in close proximity or when the DNA-replication fork encounters a SSB or other lesions, or at the end of chromosomes as a result of impaired metabolism of telomeres. Of the many types of DNA damage, DSB are probably the most lethal[2-4]. In metazoa, just one DSB can result in cell death if it inactivates an essential gene and causes apoptosis[5]. Furthermore, DSBs are of importance because they are difficult to repair, and have been associated with induction of mutations and chromosomal translocations.

For the myriad of DNA lesions, there are many distinct DNA repair mechanisms. For DSB repair, two mechanisms are used: non-homologous end-joining (NHEJ) and homologous recombination (HR). These are distinct but complimentary pathways which function to repair DSBs. In NHEJ, DSBs are recognized by the Ku protein that then binds and recruits protein kinase DNA-PKcs, leading to recruitment of Xrcc4 DNA ligase IV. This process results in ligation of two DNA DSBs and does not require extensive sequence homology[6]. There is often some limited processing or DNA polymerization which takes place before NHEJ occurs, which is error prone and results in deletions of DNA sequence. HR is initiated by ssDNA generation, which is promoted by various proteins including the MRE11-RAD50-NBS1 (MRN) complex. RAD51, BRCA1 and BRCA2 catalyze ssDNA invades undamaged template and, following the actions of polymerases, nucleases, helicases and other components, DNA ligation and substrate resolution ensue. HR is also used to restart stalled replication forks and to repair interstrand DNA crosslinks.

1.2 Homologous Recombination Defects

BRCA1 and BRCA2 genes encode protein(s) that are involved in repair of DNA double-strand breaks and cross-linking DNA damage including those induced by various chemotherapy agents through the homologous recombination pathway. DNA damage leads to localization of BRCA tumor suppressors to the nucleus, formation of RAD51 foci and subsequent DNA damage repair[7-8]. Therefore, the functional status of BRCA genes is thought to impact sensitivity to chemotherapy. The sensitivity of BRCA-deficient cells to PARP inhibition may be more related to a defect in homologous recombination by gene conversion (loss or depletion of several other HR-related genes), rather than directly due to BRCA 1/2 deficiency[9].

Beyond BRCA 1 and 2 mutations, defects in homologous recombination repair can also be caused by loss of function of proteins, including the RecA homologue RAD51, ataxia telangiectasia mutated (ATM), ataxia telangiectasia and Rad3 related (ATR), and checkpoint kinase 1 and 2 homologue (CHEK1 and CHEK2) proteins, as well as components of the Fanconi's anemia repair pathway. The inactivation of these various genes, which participate in the precise repair of breaks in double-stranded DNA by homologous recombination, lead to development of breast and other cancers. The process is initiated when ATM and CHEK2 protein kinases phosphorylate proteins such as BRCA1, which signals double stranded breaks in DNA and causes BRCA1 to localize to the site of DNA repair. BRCA2 carries the DNA-recombination enzyme RAD51 to the same site. The cascade of activity of these proteins ultimately leads to error-free DNA repair by recombination[10].

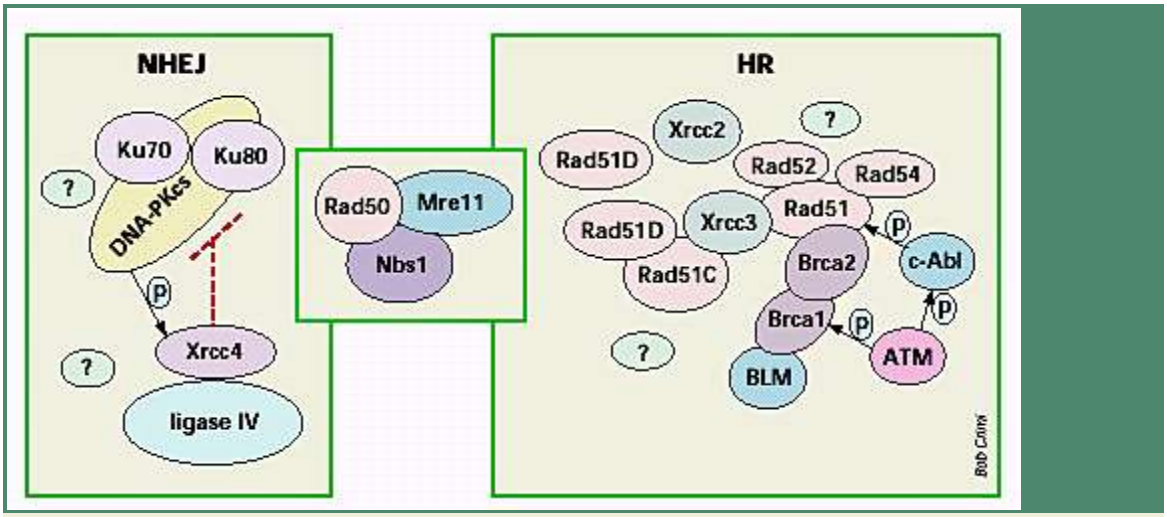

Figure 4. Components of DNA DSB repair pathways.
NHEJ: Ku binds a DSB, followed by recruitment and activation of DNA-PKcs. XRCC4 and ligase IV are recruited directly or indirectly by the DNA-PK holoenzyme and/or are activated by DNA-PK−mediated phosphorylation. HR: proteins involved in mammals are indicated. The strand-exchange reaction catalyzed by Rad51 is facilitated by Rad52 through direct interaction. Rad54, a DNA-dependent ATPase, also interacts directly with Rad51 and stimulates its activity. Rad51-related proteins (Rad51B-D, Xrcc2 and Xrcc3) are also involved in HR. There is a direct interaction between Xrcc3 and Rad51, and Rad51B and Xrcc3 interact with Rad51C. Rad51 also interacts with Brca2 and indirectly with Brca1 through Brca2. The c-Abl tyrosine kinase modulates Rad51 strand exchange activity through phosphorylation. Brca1 and c-Abl are phosphorylated by ATM. The Mre11/Rad50/Nbs1 complex, which participates in both NHEJ and HR, is also indicated.

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RAD51 is a protein that plays a major role in homologous recombination of DNA during double-strand break repair[11]. It localizes to the DNA replication fork and stimulates a DNA strand exchange reaction between homologous sequences. RAD51 mutants are associated with dysfunction in replication and repair mechanisms, chromosomal aberrations, and high sensitivity to cell death by cross-linking agents such as mitomycin C and cisplatin[12-13]. RAD51 interacts directly with XRCC2, XRCC3, BRCA1, and BRCA2 to form complexes that allow for DNA damage repair via the homologous recombination pathway, and that promote chromosomal stability. Mutations in different components of these complexes can lead to defective homologous recombination and generate a high-risk environment for cancer development. For example, XRCC2 mutations have been associated with a significantly increased risk of breast cancer[14].

ATM and ATR are members of the phosphoinositol 3-kinase–related kinase family and are involved in mediating the cellular response to double strand DNA breaks and replication dysfunction. Deficiencies in ATM and reduction of ATR kinase activity result in defects in homologous recombination[15-16]. Heterozygous ATM mutation carriers have shown an association with a moderately increased risk of breast cancer[17-18]. Studies have elucidated a potential role of ATR mutations in endometrial, colorectal and gastric cancer subsets with microsatellite instability[19]. In endometrial cancer, truncated ATR mutations are associated with a naturally more aggressive disease biology shown by significantly reduced disease-free and overall survival[20].

Fanconi anemia is a genetic disease associated with a greatly increased risk of cancer. In response to DNA damage, several Fanconi anemia proteins (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, and FANCM) form a nuclear core complex, which interacts with FANCL and leads to FANCD2 monoubiquitination. This process is integral for the repair of DNA and the accumulation of FANCD2 at sites of DNA damage where it interacts with BRCA1 and BRCA2[16,21-25]. Cells with defects in Fanconi anemia genes including FANCA, FANCC, FANCG, or FANCD2 have demonstrated deficient homologous recombination[26-29].

The partner and localizer of BRCA2 (PALB2) gene (also known as FANCN) encodes a protein that binds to and co-localizes with BRCA2 in nuclear foci, promotes its stabilization and enables DNA repair[30-31]. PALB2 also

regulates the interaction between BRCA1 and BRCA2[32]. Similar to BRCA2 mutants, PALB2-deficient cells demonstrate decreased homologous recombination capability and hypersensitivity to cross-linking agents[33]. Furthermore, PALB2-deficient cells have demonstrated sensitivity to PARP inhibitors[34]. Biallelic germline loss-of-function mutations in PALB2 cause Fanconi's anemia, whereas monoallelic mutations are associated with an increased risk of breast cancer and pancreatic cancer[35-39].

Similar to PALB2, Abraxas (FAM175), BRCA1-associated RING domain (BARD1), and BRCA1 interacting protein C-terminal helicase 1 (BRIP1) have been identified as an important genes involved in BRCA1/2 DNA damage repair and homologous recombination. Abraxas, BARD1, Rap80, and BRCA1 form a complex that engages at sites of DNA damage and is dedicated to ubiquitin chain recognition and hydrolysis at DNA DSBs via the homologous recombination pathway[40]. BRIP1 is a Fanconi anemia group protein which also interacts with BRCA1/2 in homologous recombination, with BRCA1/2 serving as the scaffolding protein[41]. Germline mutations in BRIP1 have been associated with an increased risk of epithelial ovarian cancer[42].

BRCA1-binding protein BRCA1-associated deubiquitylase (BAP1) is a deubiquitinating enzyme with C-terminal active hydrolase domain (UCH) and N-terminal nuclear localization signals (NLS1, NLS2) and is mutated in several cancers, most notably mesothelioma and melanoma, where it is thought to promote oncogenesis. BAP1 mediates PARP-dependent recruitment of the polycomb deubiquitylase complex PR-DUB to sites of DNA damage. BAP1 also serves as a phosphorylation target for the DDR kinase ATM. BAP1 promotes repair of DNA double-strand breaks, enhancing cell survival after DNA damage[43]. Given this role in DNA repair, we hypothesize those tumors which harbor this mutation may be amenable to platinum based chemotherapy.

MRE11A forms the MRN protein complex with RAD50 and NBN that initially processes and resects damaged DNA to allow for DNA repair by the homologous recombination repair pathway. In patients with mutations in MRE11A, for example, there is a higher frequency of cancers in comparison to the general population and this mutation has been linked to the Ataxia-Telangectasia-Like Disorder. In mouse models, MRE11A mutations are associated with extensive oncogene-induced breast mammary hyperplasia with frequent progression to invasive breast cancer[44]. *In vitro*, loss of the MRE11 protein has been shown to predict sensitivity to PARP-inhibitor therapy[45].

Both WRN and BLM are also involved in the MRN complex and its role in DNA damage resection via HR repair, accumulating at sites of DSBs in human cells[46]. In patients with Werner syndrome, in which they have an inherited mutation in the WRN gene, this defect is manifested as severe premature aging due to severe genomic instability[47].

CDKN1A plays an essential role in DNA damage repair, by direct inhibition of DNA replication, inducing cell cycle arrest, and by regulation of apoptosis and transcription. These functions are performed through the ability of p21 to interact with a number of proteins involved in these processes. Despite an initial controversy, during the last years several lines of evidence have also indicated that p21 may be directly involved in DNA repair. In particular, the participation of p21 in nucleotide excision repair (NER), base excision repair (BER), and DNA translesion synthesis (TLS)[48]. CDKN2A overexpression impairs the recruitment of RAD51 to the site of DNA damage by downregulating cyclin D1 protein expression. Studies have shown decreased expression of cyclin D1 in CDKN2a overexpressing cells impaired the recruitment of RAD51 to damaged DNA and impeded the homologous recombination DNA repair[49].

ATRX (alpha thalassemia/mental retardation X-linked) is a choramtin remodeler, and mutations in this gene cause alternating length of telomeres. The resulting persistent telomere cohesion promotes recombination between sister telomeres, while it suppresses inappropriate recombination between non-sisters. Forced resolution of sister telomere cohesion induces excessive recombination between non-homologs, genomic instability, and therefore inadequate DNA repair[50].

ARID1A is a member of the SWI-SNF chromatin remodeling complex which plays a role in various cellular processes including development, differentiation, proliferation, DNA repair and tumor suppression[51]. The complex uses the energy of ATP hydrolysis to facilitate access of transcription factors to regulatory DNA sequences. BAF250a is the protein encoded by ARID1A and is a subunit of the SWI-SNF complex thought to

contribute specificity to gene expression regulation [52-53]. It has been postulated that ARID1A has tumor suppressor function; ARID1A rearrangement has been shown in a breast cancer cell line, and an ARID1A deletion has been observed in a lung cancer cell line[54]. ARID1a is mutated in ~50% of ovarian clear cell carcinomas, 30% of endometriosis-associated ovarian carcinomas, and 40% of uterine low-grade endometrioid carcinomas[55-57]. ARID1A mutations have also been described in gastric, hepatocellular, breast, pancreatic, colorectal and prostate cancer[58-61].

The MLL2 gene encodes a protein which functions as a histone methyltransferase that methylates the Lys-4 position of histone H3, and is part of a multi-protein complex involved in gene regulation (beta-globin and estrogen receptor genes) and embryonic development[62-64]. In vitro, MLL2 complex has been shown to associate with Pax7, a transcription factor, and activate myogenic genes through H3 K4 methylation[65]. In vivo, MLL2 is shown to be required for normal embryonic development in mice[66]. MLL2 plays a role in regulation of gene expression programs related to cell proliferation and invasion[67] and altered expression of MLL2 is seen in human breast and colon tumors[68]. Additionally, studies have shown that aberrations in histone lysine methylation may have clinical relevance to breast, ovarian, and pancreatic cancer[69].

SLX4 is involved in homologous recombination in several ways and serves as an important scaffold for proteins involved in the repair of damaged DNA via homologous recombination[70]. Biallelic mutations in SLX4 have been seen in patients with Fanconi anemia and hereditary breast cancer[71].

The role of PTEN in homologous recombination is less clear, but it is responsible for phosphorylation of AKT substrates including CHEK1, which in turn is responsible for delaying cell cycle progression to allow for DNA damage repair. *In vitro*, PTEN-deficient cell lines are hypersensitive to PARP inhibitors, highlighting its role in homologous recombination[72].

1.3 PARP Inhibition

Poly (ADP-ribose) polymerase (PARP) is an enzyme involved in DNA base excision repair via binding to single-strand breaks in DNA and bringing DNA repair proteins to the damaged site[73]. The mechanisms of action of PARP inhibitors include trapping of PARP enzyme on DNA and inhibition of base excision repair, leading to induction of DSBs[74-76]. Thus PARP inhibition results in less efficient DNA repair following a cytotoxic insult. DNA damaging agents, including cytotoxic chemotherapy and radiation therapy, remain a mainstay of cancer therapy, and cancer cells are often genetically unstable and/or exhibit deficiencies in DNA repair systems[77-78]. These deficiencies render cells more dependent on PARP for DNA repair and thus more sensitive to PARP inhibition[78]. Additionally, higher expression of PARP in cancer cells compared to normal cells has been linked to drug resistance and the overall ability of cancer cells to sustain genotoxic stress[79]. Consequently, PARP inhibitors are proposed as sensitizing agents for ionizing radiation therapy and a variety of DNA-damaging agents including platinums, alkylators, and topoisomerase inhibitors.

Tumors which are characterized by a defect in homologous DNA repair function, including germline or somatic BRCA 1/2 mutations, appear to be susceptible to PARP inhibitors[74].

Studies in breast and ovarian cancers with BRCA 1/2 mutations have demonstrated tumor responses and progression-free survival benefit with olaparib and other PARP inhibitors[80-85]. In patients with ovarian cancer, an association between platinum sensitivity and extent of olaparib response has been observed[86]. Furthermore, there have been reports of responses to PARP inhibitors in BRCA 1/2-mutated prostate and pancreatic cancers[87-88].

1.3.1 PARP Inhibition in Breast Cancer

In a 2010 Lancet article, Tutt et al described the clinical efficacy of olaparib, which was demonstrated in a Phase 2 study including 54 patients with BRCA carriers with advanced breast cancer who had received a median of 3 prior chemotherapy regimens to be efficacious. The ORR was 41% (11/27 patients) in the cohort assigned to 400 mg twice daily, and 22% (6/27) in the cohort assigned to 100 mg twice daily. Median duration of response was ~140 days[80].

1.3.2 PARP Inhibition in Ovarian Cancer

Data supporting the activity of PARP inhibitors in BRCA mutant ovarian cancer is steadily growing. In December 2014, olaparib was approved as monotherapy for the treatment of patients with germline BRCA mutated advanced ovarian cancer who have previously received three or more lines of chemotherapy[89-90]. In a larger cohort of patients with ovarian cancer (n=193) published in JCO by Kaufman et al, the tumor response rate was 31.1%, the median progression-free survival was 7 months, and median overall survival was 16.6 months. Tumor response rates for breast, pancreatic, and prostate cancers were 12.9% (8/62; 95% CI, 5.7-23.9), 21.7% (5/23; 95% CI, 7.5-43.7), and 50.0% (4/8; 95% CI, 15.7-84.3) respectively[91].

The NOVA study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of niraparib (administered once daily continuously during a 28-day cycle) as maintenance in platinum-sensitive ovarian cancer patients who have either gBRCA mutation or a tumor with high-grade serous histology and who have responded to their most recent platinum-containing chemotherapy regimen. Design of these two independent cohorts is based on the hypothesis that patients with gBRCA mutations have more pronounced responses to niraparib. Primary endpoint is PFS[92].

1.3.3 PARP Inhibition in Other Malignancies

A durable antitumor effect with PARP inhibitors has been seen in metastatic castrate-resistant prostate cancer and germline BRCA2 mutations[85,87,93]. A study published in the New England Journal of Medicine in October 2015 by Mateo et al demonstrated that in patients with prostate cancer whose tumors were no longer responding to standard therapies and harbored defects in DNA-repair genes (including BRCA 1/2, ATM, Fanconi's anemia genes and CHEK2), treatment with olaparib led to a high response rate (88%)[94].

1.3.4 PARP Inhibition Effect on Homologous Recombination

The loss of DNA homologous recombination repair mechanism (homologous recombination deficiency) leads to genomic instability and culminates in tumor cell growth[95-96]. The development of this deficiency can be due to loss of function or inactivation of genes involved in DNA repair as described above including BRCA 1/2, RAD51 or ATM. In a tumor cell which is already affected by one of these deleterious mutations, PARP inhibitors will exploit this mechanism, and effectively lead to cell death by the accumulation of genomic aberrations and defective DNA repair. This concept, where two pathway defects alone can be tolerated but when combined become lethal is known as synthetic lethality[74-75,97]. Homologous recombination deficiency is more common in ovarian cancers compared to BRCA1/2 mutations, 40-50% versus 15% respectively[98]. Causative factors in the case of homologous recombination deficiency include somatic BRCA 1/2 mutations, BRCA1 methylation (which leads to inactivation of the gene), and mutations in other genes implicated in the DNA repair via homologous recombination pathway[98-99]. Thus, there is a clinical need to uncover those biomarkers that can identify patients whose tumors may respond better to PARP inhibition.

In a 2006 study by McCabe et al, the hypothesis that other tumors deficient in integral HR genes would also be sensitive to PARP inhibitors. They were able to show deficiency of RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHK1, CHK2, FANCD2, FANCA, or FANCC induces such sensitivity[10].

1.3.5 PARP Inhibition in Addition to Chemotherapy

While single agent PARP inhibitors have been effective in breast and ovarian cancer, the addition of chemotherapy may provide more benefit and certain cancer types may require chemo. The activity of combined olaparib and chemotherapy was investigated in a randomized Phase 2 study in patients with platinum sensitive, recurrent, high-grade serous ovarian cancer who had received up to 3 previous courses of platinum-based chemotherapy and were progression-free for at least 6 months. Pts were randomized in a 1:1 fashion to either olaparib plus chemotherapy then olaparib monotherapy (olaparib plus chemotherapy group) or chemotherapy alone. Primary endpoint was PFS, and prespecified exploratory analyses included efficacy by BRCA mutations status. PFS was significantly longer in the olaparib plus chemotherapy group (median 12.2 months) than in the chemotherapy alone group (median 9.6 months), especially in patients with BRCA mutations.

In the combination phase, adverse events that were reported at least 10% more frequently with olaparib plus chemotherapy than with chemotherapy included alopecia, nausea, neutropenia, diarrhea , headache, peripheral neuropathy, and dyspepsia. Most were of mild-to-moderate intensity. The most common grade 3 or higher

adverse events during the combination phase were neutropenia (in 43% of 81 patients in the olaparib plus chemotherapy group versus 35% of 75 in the chemotherapy alone and anemia (0% versus 7%, respectively). Serious adverse events were reported in 12 (15%) of 81 patients in the olaparib plus chemotherapy group and 16 of 75 (21%) patients in the chemotherapy alone group[84].

1.3.6 PARP Inhibition Resistance

Though there is great enthusiasm for the benefit of PARP inhibitor-based therapy in patients with metastatic breast cancer who are BRCA1 or -2 mutation carriers, it is clear that not all patients benefit, and all eventually develop tumor progression. Thus there are both intrinsic and acquired mechanisms of resistance. The mechanisms underlying responsiveness to treatment are critical to further identifying candidates for this therapy, as well as opening potential avenues to overcome resistance to these agents.

Secondary BRCA mutations have been reported and have been shown to restore BRCA function. In the study by Norquist et al, six carboplatin-resistant patients with ovarian cancer carrying BRCA mutations were subsequently treated with the PARP inhibitor olaparib. Of these patients, two exhibited de novo resistance to olaparib, two showed a partial response (PR) and two showed a complete response (CR). The patients who were de novo resistant to olaparib both had secondary mutations, one with reversion to the wild-type allele and one with a 1-bp insertion; both of these mutations restored the BRCA2 open reading frame. Of the two patients with a PR, one exhibited a reversion of a BRCA2 allele to the wild-type sequence, whereas the other was not found to have a secondary BRCA2 mutation. The two patients who showed a CR to olaparib did not show any signs of secondary mutation[100].

There are preclinical models which also suggest one mechanism of resistance to PARP inhibitor olaparib was conferred by increased efflux of the drug by ABC transporter P-glycoprotein (PgP) due to increased expression of PgP. This was supported by studies in mice which showed enhanced long-term response to PARP inhibition when PgP was genetically inactive. Newer PARP inhibitors (AZD2461) which were poor PgP substrates showed improved antitumor response compared to response with olaparib[101].

Reduced/absent 53BP1 expressions results in partial restoration of HR. Loss of 53BP1 was identified by immunohistochemistry in 3 of 11 olaparib-resistant tumors and in 3 of 12 AZD2461-resistant tumors. Expression loss was explained by truncating mutations, duplications, frame-shifts, and silencing. This was supported by previous in vitro studies loss of 53BP1 partially restores the HR defect that BRCA-1 deletion confers[102].

A more recent article by Choi et al suggested that resistance mechanism by which a microRNA, miR-622, induces resistance to PARP inhibitors and platinum in *BRCA1* mutant HGSOCs by targeting the Ku complex and restoring HR-mediated DSB repair. Physiologically, miR-622 inversely correlates with Ku expression during the cell cycle, suppressing non-homologous end-joining and facilitating HR-mediated DSB repair in S phase. Importantly, high expression of miR-622 in *BRCA1*-deficient HGSOCs is associated with worse outcome after platinum chemotherapy, indicating microRNA-mediated resistance through HR rescue[103].

1.4 Niraparib Activity and Pharmacokinetic Profile[104]

1.4.1 Niraparib Overview

Please refer to the most recent Investigator Brochure for the current information on Niraparib.

Niraparib (formerly MK-4827) is an oral small molecule, selective inhibitor of PARP-1 and PARP-2. PARP-1/PARP-2 are zinc-finger DNA-binding enzymes that are activated by binding to DNA double- or single-strand breaks, leading to the conversion of DNA damage into intracellular signals that either activate DNA repair by the base excision repair (BER) or NHEJ pathway, or triggers cell death in the presence of extensive DNA damage. In tumors with defects in homologous repair (HR), the activity of PARP-1 and PARP-2 are required for BER and NHEJ. With PARP inhibition, this alternative pathway is shut down, leading to ongoing DNA damage and ultimately cell death. PARP inhibition also leads to increased tumor cell death when combined with cytotoxic chemotherapy such as cisplatin, carboplatin, alkylating or methylating agents, radiation therapy, and topoisomerase I inhibitors; PARP activity is also required for repair of DNA damage induced by standard cytotoxic chemotherapy. As such, niraparib has been developed as a treatment for tumors with defects in the HR DNA

repair pathway, as well as a sensitizing agent in combination with cytotoxic agents and radiotherapy. In Phase I clinical testing, niraparib is generally safe and well tolerated.

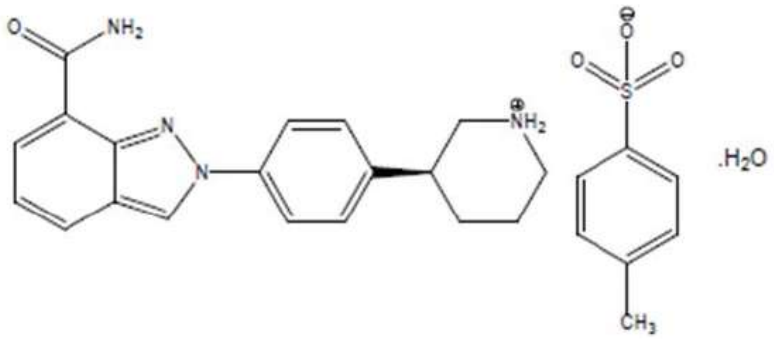

Figure 5. Chemical structure of niraparib

1.4.2 Niraparib *in vitro* Pharmacology

[redacted]

1.4.3 Niraparib *in vivo* Pharmacology

[redacted]

[redacted]

More recently, the combination of niraparib with irinotecan was studied in microsatellite instable (MSI) and microsatellite stable (MSS) colorectal cancer (CRC) models, and the combination was shown to be more efficacious than irinotecan or niraparib alone in both MSI and MSS CRC cell lines. In this evaluation, mice were given 10, 25, or 50mg/kg daily of niraparib for 3, 5, or 7 days alone or in combination with 100mg/kg irinotecan intraperitoneally weekly for 4 weeks. Mice that received both study drugs had an average tumor volume at the end of the study period of 120mm^3 in the highest niraparib dose group versus 225mm^3 with irinotecan alone[105].

[redacted]

1.4.4 Non-clinical Pharmacokinetics and Metabolism of Niraparib

[redacted]

[redacted]

1.4.5 Human Pharmacokinetics, Metabolism and Efficacy of Niraparib

[redacted]

1.4.5.1 Phase I Niraparib Data

[redacted]

1.4.5.1.1 Niraparib Monotherapy

[redacted]

[redacted]

1.4.5.1.2 Niraparib Combination Therapy

[redacted]

[redacted]

[redacted]

1.4.5.2 Phase II Niraparib Data

[redacted]

1.4.5.2.1 Niraparib Monotherapy

[redacted]

1.4.5.3 Phase III Niraparib Data

[redacted]

1.4.5.3.1 Niraparib Monotherapy

[redacted]

1.4.6 Safety Pharmacology and Toxicity of Niraparib

[redacted]

[redacted]

[redacted]

[redacted]

1.5 Carboplatin[106]

Platinum agents, which have been shown to have broad antitumor activity in solid tumors, are alkylating agents which bind to and crosslink DNA. The platinum-DNA adducts then impedes cellular processes including replication and transcription, preventing DNA-strand separation. Cisplatin was the first member of the platinum family to be discovered to carry antitumor effects and was FDA-approved for that purpose in 1978. Cisplatin use, however, has been limited by its toxicity profile, namely nephrotoxicity and gastrointestinal toxicity, and therefore safer platinum salts were sought. Carboplatin is a more stable and safer analog of cisplatin and has been shown to have similar antitumor activity and efficacy in a variety of different cancer subtypes with essentially no nephrotoxic and less gastrointestinal and neurotoxicity. Tumors containing deleterious DNA repair mutations, such as BRCA1 or BRCA2 mutations, have been shown to be more sensitive to DNA-damaging agents, including platinums[107].

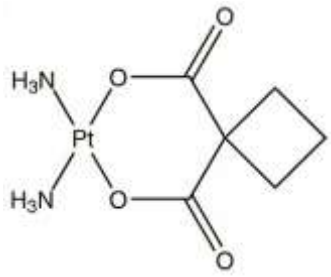

Figure 6. Chemical structure of carboplatin

1.5.1 Carboplatin Pharmacokinetics

In patients with creatinine clearances of 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 mg/m^2 to 500 mg/m^2. The initial plasma half-life was found to be 1.1 to 2 hours, and the post-distribution plasma half-life was found to be 2.6 to 5.9 hours. The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4 L/hour,

16L and 3.5 hours, respectively. The C_{max} values and areas under the plasma concentration versus time curves from 0 to infinity (AUC_{inf}) increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300 mg/m-500 mg/m).

Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days. The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3% to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages should be reduced in these patients.

1.5.2 Human Efficacy and Safety of Carboplatin

The efficacy and safety of carboplatin has been studied in a variety of different cancer subtypes. Carboplatin is currently FDA-approved in both the first and second-line setting for advanced ovarian carcinoma (in combination with cyclophosphamide in first-line), with evidence of improved overall survival. Treatment in studied patients was complicated by emesis, hypersensitivity reactions, dose-dependent bone marrow suppression, and peripheral neuropathy – particularly in patients over 65 years. Because carboplatin clearance is dependent on creatinine clearance, carboplatin doses were reduced to 250mg/m^2 (from 300mg/m^2) for a creatinine clearance of 41-59 mL/min and 200mg/m^2 for a creatinine clearance of 16-40 mL/min. In single-agent use in the second-line setting, carboplatin is administered with a target AUC of 4-6. Carboplatin is also used off-label in combination with other chemotherapy agents in breast, bladder, cervical, endometrial, esophageal, head and neck, melanoma, lymphoma, non-small cell lung, sarcoma, small-cell lung, testicular, and thymic cancers with similar side effect profiles and AUC goals, adjusted for creatinine clearance.

1.6 Rationale for Current Study

Patients with deleterious DNA repair mutations have been shown to be more sensitive to DNA-damaging agents including platinums, and the addition of PARP inhibition in these patients is thought to further sensitize cancer cells to the effects of DNA-damaging chemotherapeutic agents. Niraparib is one such PARP inhibitor that is both safe and efficacious in patients with advanced solid tumors with HRD and/or BRCA-1/2 mutations. The effects of niraparib in combination with platinum-based chemotherapy have not yet been studied in depth, though we know from previous evaluations of PARP inhibition with platinum chemotherapy that the combination is safe and more efficacious than chemotherapy alone, particularly in HRD tumors[70]. We therefore hypothesize that using a combination of niraparib and carboplatin with close assessment of toxicity and tolerability will lead to better anti-tumor effect than either agent alone in patients with advanced solid tumor malignancies with evidence of HRD, as demonstrated by germline or somatic deleterious mutations in the homologous recombination DNA repair pathway. Efficacy of PARP inhibition may negatively correlate with the development of resistance mechanisms, and as such we plan to serially assess for the development of resistance in tumor biopsy samples over the course of study treatment.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives:

2.1.1 Phase Ia (dose-escalation phase): To identify the RP2D and schedule of niraparib plus carboplatin for patients with homologous recombination deficient advanced solid tumor malignancies

2.1.2 Phase Ib (dose-expansion phase): To determine the anti-tumor efficacy of niraparib plus carboplatin in a non-disease specific cohort of patients with homologous recombination deficient advanced solid tumor malignancies, as determined by RECIST v1.1

2.2 Secondary Objectives:

Clinical:

a. To evaluate the safety and tolerability of niraparib plus carboplatin
b. To determine evidence of any disease specificity with this combination
c. To assess the anti-tumor efficacy of combined therapy as determined by RECIST v1.1
d. To assess the anti-tumor efficacy of combined therapy as determined by measurement of overall survival (OS) and progression free survival (PFS)

Scientific:

a. To assess the effects of niraparib alone, and niraparib plus carboplatin on pharmacodynamic markers of DNA damage and repair, including γH2AX/RAD51 foci formation, and as measured by the PARP trapping assay
b. To explore predictive markers of response and/or resistance to therapy in serial tumor biopsy samples

2.3 Indication:

Patients with advanced solid tumor malignancies harboring a germline or somatic deleterious mutation in genes involved in DNA damage repair through homologous recombination (including but not limited to *RAD50/51/51B, BARD1, BLM, BRCA1, BRCA2, BRIP1, FANCA/C/D2/E/F/G/L, PALB2, or BAP1* that may benefit from molecularly targeted therapy with the PARP inhibitor, niraparib, in addition to chemotherapy with carboplatin.

3.0 SUBJECT POPULATION

3.1 Subject Population, Number of Subjects and Feasibility

(See Appendix A for Study Eligibility Checklist)

3.1.1 Subject Population

Patients will have advanced solid tumor malignancies harboring a germline or somatic deleterious mutation in genes involved in DNA damage repair through homologous recombination including but not limited to *RAD50/51/51B, BARD1, BLM, BRCA1, BRCA2, BRIP1, FANCA/C/D2/E/F/G/L, PALB2, or BAP1* and will have biopsiable disease and measurable disease by RECIST v1.1 criteria, and will have an adequate PS, bone marrow, hepatic, and renal function. In the Phase Ib portion of study, there will be one expansion cohort of 20 patients with a patient population identical to Phase Ia.

3.1.2 Number of Subjects

A minimum of 18 and a maximum of 126 evaluable patients for Phase Ia, and 20 evaluable patients for Phase Ib.

3.1.3 Feasibility

At the multiple sites participating in this study, we anticipate being able to screen as many as 1,000 patients per year. Assuming a qualifying mutation rate of 5-10%, and 25% of screened patients being otherwise trial eligible, we anticipate enrolling 30 patients per year across multiple medical institutions within the United States. Only patients with advanced solid tumor malignancies will be eligible for enrollment. The expected accrual duration will be approximately 48 - 60 months.

3.2 Inclusion Criteria

3.2.1 Patients PRE-identified as having either a germline deleterious mutation or tumor expression of a deleterious mutation) as determined by Next-generation DNA sequencing only, in at least one gene involved in DNA damage repair through homologous recombination including but not limited to: *RAD50/51/51B, BARD1, BLM, BRCA1, BRCA2, BRIP1, FANCA/C/D2/E/F/G/L, PALB2, or BAP1.*

3.2.1.1 Patients with somatic mutations will be PRE-identified as having a homologous recombination mutation based on NGS done in a CLIA certified, CAP tested and bioinformatics-validated testing lab PRIOR to enrollment in this current protocol. The testing may have been done at any time prior to enrollment.

3.2.1.1.a The determination of a deleterious mutation must be supported in the documentation included in the testing, and should include clinical, or pre-clinical literature to support the finding that a specific mutation results in impaired function of the gene, and thus impaired DNA repair through homologous recombination. Variants of unknown significance will not be eligible.

3.2.1.1.b For the Phase Ib portion of the study, if any patient has had NGS testing more than 12 months prior to enrollment, then a repeat NGS test must be done and the deleterious somatic mutation must be re-identified for inclusion.

3.2.1.2 Patients with germline deleterious mutations may have been identified at any time point prior to inclusion in the protocol and do NOT need to have this genetic testing repeated regardless of time frame and intervening therapy.

3.2.2 Advanced, solid tumor malignancy (other than prostate cancer, see Section 3.3.11).

3.2.2.1 The tumor must be amenable to biopsy.

3.2.2.2 For the Phase Ib portion, the patient must consent to 4 mandatory biopsies during study.

Note: If there are any issues with obtaining the study required pre-treatment biopsy (ie. it is deemed unsafe to obtain the biopsy or it is determined that the initial biopsy sample obtained did not contain tumor tissue), the subject may only be allowed to enroll after receiving permission from the Study Chair(s). Additionally, they will be exempt from being required to obtain additional on study biopsies.

3.2.3 Life expectancy of more than 3 months

3.2.4 Age ≥ 18 years

3.2.5 Measurable disease by RECIST v1.1 criteria (tumor ≥ 1 cm in longest diameter on axial image on computed tomography (CT) or magnetic resonance imaging (MRI) and/or lymph node(s) ≥ 1.5 cm in short axis on CT or MRI) on baseline imaging

3.2.6 ECOG performance status (PS) of 0 to 1 (Table 11, Appendix A)

3.2.7 Patients who have received and experienced disease progression on, or have been intolerant to, standard first line therapies known to confer clinical benefit. Patients who refuse standard therapy would also be eligible, as long as their refusal is documented.

3.2.8 Adequate hepatic, bone marrow, and renal function at the time of enrollment:

3.2.8.1 Bone Marrow: Absolute neutrophil count (ANC) ≥ 1,500/mm^3; Platelets ≥ 100,000/mm^3; Hemoglobin ≥ 9.0 g/dL. Patients must be able to meet the criteria without transfusion within 4 weeks or receipt of colony stimulating factors, filgrastim (eg neupogen or biosimilar) within 14 days, or peg-filgrastim (eg, neulasta) or recombinant erythropoietin within 4 weeks before obtaining sample

3.2.8.2 Renal function: Serum creatinine ≤ 2.0 mg/dL **OR** creatinine clearance ≥ 50 mL/min/1.73 m^2

3.2.8.3 Hepatic function: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × the upper normal limit of institution's normal range. Total bilirubin ≤ 1.5 × the upper normal limit of institution's normal range. For subjects with liver metastases, AST and ALT ≤ 5 × the upper normal limit of institution's normal range, and total bilirubin >1.5 - 3.0 x the upper normal limit of institution's normal range are acceptable as long as there is no persistent nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

3.2.8.4 Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) must be ≤ 2 X the upper limit of the institution's normal range and International Normalized Ratio (INR) < 2. Subjects on anticoagulation (such as coumadin) will be permitted to enroll as long as the INR is in the acceptable therapeutic range as determined by the investigator

3.2.9 Patients may have received an unlimited number of prior therapies. Prior anti-cancer therapies must be given ≥ 2 weeks prior to Cycle 1, Day 1 on trial (and the patient must have recovered from all side effects of prior therapies that are exclusionary, as per Section 3.3 below)

3.2.10 Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring conscious sedation such as endoscopies or mediport placement may only require a 24-hour waiting period, but this must be discussed with an investigator

3.2.11 Female patient has a negative serum or urine pregnancy test within 72 hours prior to taking study treatment if of childbearing potential and agrees to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment, or is of non-childbearing potential. Non-childbearing potential is defined as follows (by other than medical reasons):

- ≥45 years of age and has not had menses for >1 year
- Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
- Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure

Otherwise the patient must be willing to employ methods to avoid pregnancy. Abstinence is an acceptable method to avoid pregnancy if this is the established and preferred method for the patient. Alternatively, the patient and partner must use 2 adequate barrier methods throughout the study, starting with the screening visit

through 180 days after the last dose of study treatment. Information must be captured appropriately within the site's source documents.

Male patients must also agree to use an adequate method to avoid pregnancy, which may include abstinence, if this is the established and preferred method for the patient starting with the first dose of study treatment through 180 days after the last dose of study treatment.

Additionally, the participants must agree to not breastfeed during the study or for 180 days after the last dose of study treatment.

3.2.12 Patient is capable of swallowing pills whole

3.2.13 Subject is capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the IRB, prior to the initiation of any screening or study-specific procedures

3.3 Exclusion Criteria

3.3.1 Prior disease progression while receiving platinum chemotherapy; or any platinum chemotherapy within the last 6 months

3.3.1.1 For all patients (except breast cancer patients) who received platinum-based adjuvant or neo-adjuvant chemotherapy, at least 6 months must have passed between the last dose of platinum-based therapy and the development of metastatic disease.

3.3.1.2 For breast cancer patients, at least 12 months must have passed between the last dose of platinum-based adjuvant or neo-adjuvant therapy and the development of metastatic disease

3.3.2 Patients must not require "support" to maintain adequate blood counts, as defined by:

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

3.3.1.2 Patient must not have received colony stimulating factors, filgrastim (eg neupogen or biosimilar) within 14 days, or peg-filgrastim (eg, neulasta) or recombinant erythropoietin within 4 weeks prior initiating protocol therapy.

3.3.2.1 Participant has had any known Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment.

3.3.3 Prior PARP inhibitor-based therapy

3.3.4 Known or suspected CNS metastases, unless at least one month has passed since last local CNS therapy and there is no evidence for recurrent or progressive CNS disease on follow up imaging. Participants may remain on steroids for CNS disease if they are taking a stable dose

3.3.5 Active severe infection, or known chronic infection with HIV or hepatitis B virus (testing not required prior to enrollment)

3.3.5.1 Patients with chronic Hepatitis C virus *may* be enrolled if there is no clinical/laboratory evidence of cirrhosis AND the patient's liver function tests fall within the parameters set in Section 3.2.8.3, Inclusion Criteria, Hepatic function

3.3.6 Cardiovascular disease problems including unstable angina, therapy for life-threatening ventricular arrhythmia, or myocardial infarction, stroke, or congestive heart failure within the last 6 months.

3.3.7 Life-threatening visceral disease or other severe concurrent disease that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.)

3.3.8 Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)

3.3.9 Presence of a psychiatric illness or social situation that would limit compliance with study requirements

3.3.10 Women who are pregnant or breastfeeding

3.3.11 The subject must not have had diagnosis, detection, or treatment of another type of cancer ≤2 years prior to randomization (except basal or squamous cell carcinoma of the skin that has been definitively treated). Questions regarding the inclusion of individual subjects should be directed to the Principal Investigator, Dr. Isaacs.

3.3.12 Due to licensing agreements for Niraparib, patients with a current diagnosis of prostate cancer will be excluded.

3.3.13 Clinically significant peripheral neuropathy at the time of enrollment (defined in the NCI CTCAE v4.0) as grade 2 or greater neurosensory or neuromotor toxicity)

3.3.14 Patients must not have had investigational therapy administered ≤4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study

3.3.15 Patients must not have had radiotherapy encompassing >20% of the bone marrow within 2 weeks; or any radiation therapy within 1 week prior to Day 1 of protocol therapy

3.3.16 Patients must not have a known hypersensitivity to the components of niraparib or the excipients

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

3.3.18 Patients must not be considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent

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

3.4 Additional Study Restrictions

3.4.1 Granulocyte Colony-Stimulating Factor (GCSF)

Prophylactic cytokine (Granulocyte Colony-Stimulating Factor [GCSF]) administration should not be given in the first cycle of the study, but may be administered in subsequent cycles according to local guidelines and Section.

3.4.2 Substrates of P-glycoprotein

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

3.4.3 Other Anticancer Therapy

For purposes of this protocol, anti-tumor treatment may be defined as, but is not limited to, anti-cancer agents (cytotoxic chemotherapy, immunotherapy, endocrine therapy, or biologic therapy), radiotherapy, and investigational agents. An investigational agent is any drug or therapy not currently approved for use in humans. No other anticancer therapy is permitted during the course of the study treatment for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to enrollment, per exclusion criteria above). If the patient discontinues study treatment, this restriction no longer applies, however the patient will remain enrolled in the study for the purpose of collecting subsequent outcomes. ***Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing >20% of the bone marrow within 2 weeks of the first dose of study treatment) is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present >1 week prior to first dose of study treatment.***

3.4.4 Vaccines

Live vaccines within 7 days prior to the first dose of study treatment. Seasonal flu vaccines that do not contain live viruses are allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, bacille Calmette Guerin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines and are not allowed

3.4.5 Birth Control

An adequate method of birth control should be used from the time the participant signs the consent form, the duration of protocol therapy, and for 180 days following the last dose of niraparib. Acceptable methods of birth control include:

- Total sexual abstinence
- Two highly effective forms of contraception, defined as: diaphragm, condom (male or female), sponge, and/or spermicide per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).
- Permanent sterilization, defined as hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral orchiectomy. Participants and their sexual partners who've undergone vasectomy or tubal occlusion must also use a male condom with spermicide.
- Postmenopausal, defined as a female participant or sexual partner >45 years of age who has not menstruated for at least 12 consecutive months

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

3.4.6 Breast Feeding

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

3.4.7 Blood Donation

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

3.5 Other Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at Screening up to the Final Visit must be recorded in source documents and the case report forms (CRFs). The reason for use, date(s) of administration (including start and end dates), and dosage information (including dose and frequency) must be recorded. Any change in concomitant therapy during the study period must be similarly recorded. Questions regarding prior or concomitant therapy should be directed to one of the investigators.

3.5.1 Prior Surgery

Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring conscious sedation such as endoscopies or mediport placement only require a 24 hour waiting period.

3.5.2 Supportive Care

Subjects should receive best supportive care and treatment of symptoms during the study as appropriate, including transfusion of blood and blood products, oxygen therapy, nutritional support, intravenous fluids, and treatment with appropriate medications (antibiotics, antiemetics, antidiarrheals, and analgesics, etc.). Medications, including steroids, which are given for supportive care, such as appetite stimulation, may be given concurrently.

3.5.2.1 Bisphosphonates and denosumab

Bisphosphonates and denosumab are permitted for the treatment of osteoporosis and prevention of skeletal related events for patients with bone metastases.

3.5.2.2 Hematopoietic growth factors

Hematopoietic growth factors may be used according to the American Society of Clinical Oncology (ASCO) guidelines, but not during the first three cycles of the Phase Ia portion of the study (Section 6.9, Table 8). The patient must be referred to a hematologist for further evaluation (1) if frequent transfusions are required or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less after 4 weeks.

3.5.3 Permitted Concomitant Therapy Requiring Caution

Medications to be used with caution during niraparib and carboplatin treatment in this study are listed below. This list is not comprehensive and is only meant to be used as a guide. These medications should be excluded from patient use if possible. If they must be given, then use with caution. There are no known absolutely contraindicated medications in combination with niraparib and carboplatin.

- Inducers of CYP1A2:
  - Moderate inducers: montelukast, phenytoin, theophylline, tizanidine, warfarin
  - Weak inducers: alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine, moricizine, omeprazole, phenobarbital
- Antiplatelet and Anticoagulation agents (combined bleeding risk if thrombocytopenia develops):
  - Antiplatelet: aspirin, triflusal, clopidogrel, prasugrel, ticagrelor, ticlopidine, cilostazol, vorapaxar, abciximab, eptifibatide, tirofiban, dipyridamole, thromboxane inhibitors
  - Anticoagulation: coumadin, dabigatran, rivaroxaban, apixaban, edoxaban, heparin, fondaparinux, bivalirudin, argatroban
- Aminoglycosides (increased risk of ototoxicity with carboplatin): tobramycin, gentamicin, streptomycin, neomycin, kanamycin

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

3.6 Removal/Replacement of Subjects from Therapy or Assessment

An evaluable patient must meet all inclusion/exclusion criteria, have adequate tissue for initial molecular assessment as well as repeat biopsies per protocol, and be evaluable for the primary study endpoints of safety and tolerability of niraparib with carboplatin as measured by NCI CTCAE 5.0 as well as anti-tumor efficacy as determined by RECIST v1.1.

3.6.1 Screen Failures

Patients will be identified and enrolled when treatment modification required (initial therapy or change in therapy for progressive disease). All patients must continue to meet the inclusion and exclusion criteria up to and including the first day of treatment. Reasons for patients who have enrolled, but become ineligible could include (but are not limited to):

- The patient is no longer eligible based on laboratory parameters
- The patient's performance status has declined
- The patient does not have adequate tissue for molecular assessment
- The patient no longer has measurable disease

Patients who become ineligible prior to initiation of therapy per protocol will be considered screen failures. Screen failures must be replaced until: 1) enough patients are enrolled to determine the RP2D and schedule in the Phase Ia portion of study; and 2) 20 patients are enrolled in the Phase Ib portion of study.

3.6.2 Evaluable Patients

3.6.2.1 Safety and Tolerability Evaluable

For the Phase Ia portion, for a patient to be evaluable for safety, tolerability, and assessment of dose-limiting toxicities, the patient must complete the first two cycles. Any patient who is taken off study for any reason other than toxicity (or death related to toxicity) ***will not be*** considered evaluable for assessment of safety, tolerability, and assessment of dose-limiting toxicity, and must be replaced.

3.6.2.2 Response Evaluable

A patient who initiates therapy per protocol, and is taken off study for disease progression or clinical progression, including death related to the underlying solid tumor malignancy (as determined by the treating oncologist) ***will be*** considered evaluable for response assessment. However, patients who have initiated therapy and who withdraw from the study for any reason other than clinical or radiographic progression, or death believed unrelated to their underlying solid tumor malignancy ***will not be*** considered evaluable for response. Reasons for patients who have initiated therapy, but are no longer evaluable for response could include (but are not limited to):

- The patient cannot tolerate therapy despite dose modifications, and there is no evidence of clinical/radiographic disease progression at the time of stopping therapy
- An unexpected and/or unrelated medical illness, such as a stroke or myocardial infarction that is considered unrelated to the underlying solid tumor malignancy
- An unexpected trauma or death that is considered unrelated to the underlying solid tumor malignancy

3.7 Multi-Institutional Trial Coordination

(See Appendix B for the Patient Registration Form)

3.7.1 Personnel

Georgetown University's LCCC Consortium IIT Office will play the primary role in coordinating the trial between Lombardi-Georgetown and additional sites. Georgetown University's LCCC Consortium IIT Office will be the main point of contact for Dr. Isaacs and the other site PIs for any study related concerns, including data management and regulatory.

3.7.2 Patient Enrollment

Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send an email within 24 hours containing the patient's initials to the local PI, to Dr. Isaacs, and to Georgetown University's LCCC Consortium IIT Office. If a patient is successfully screened, the local research coordinator must send all supporting documentation to Georgetown University's LCCC Consortium IIT Office by secure email to confirm eligibility. Patients should not start therapy until Dr. Isaacs and Georgetown University's LCCC Consortium IIT Office have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment.

3.7.3 Data Collection and Management

Patient data will be entered into the on-line accessible database. This database is housed at Lombardi-Georgetown, but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session so that they may learn how to enroll data into the data base. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within 10 business days of each patient visit.

3.7.4 Conference Calls

A monthly conference call will be held between Lombardi-Georgetown and the other sites to review patient enrollment, toxicity, and response assessment.

In addition, a separate conference call will be held between OHSU and the other sites to review sample collection, tissue coordination, and tissue analysis. This will include an ongoing review of the success rate of the tumor biopsies, and of the *ex-vivo* tumor samples.

3.7.5 Trial Auditing

Georgetown University's LCCC Consortium IIT Office will arrange all primary source documents for the patients to be audited. This will include collecting copies of the primary source data for any patients treated at other sites.

4.0 STUDY PROCEDURES: MOLECULAR ASSESSMENT AND TREATMENT ASSIGNMENT

4.1 Study Overview

This is a multi-institutional Phase I dose-escalation and dose-expansion trial for patients with advanced solid tumor malignancies and pre-identified germline or somatic deleterious mutations in the homologous recombination DNA repair pathway (HR deficient). The trial is designed to assess the efficacy and safety of niraparib plus carboplatin in patients with evidence of HRD. The primary endpoint will be identifying the RP2D and schedule of niraparib plus carboplatin, as well as establishing the anti-tumor efficacy of niraparib plus carboplatin as determined by RECIST v1.1 criterion.

Potential trial patients will be pre-identified at participating centers as having either a germline or somatic deleterious mutation involving genes critical to DNA repair through homologous recombination, as demonstrated by Next-generation DNA sequencing in a CLIA certified, CAP tested and bioinformatics-validated testing lab prior to enrollment. This could include, but not be limited to one of the following genes – *RAD50/51/51B, BARD1, BLM, BRCA1, BRCA2, BRIP1, FANCA/C/D2/E/F/G/L, PALB2, or BAP1.* The determination of a deleterious mutation must be supported in the documentation included in the testing, and should include clinical, or pre-clinical literature to support the finding that a specific mutation results in impaired function of the gene, and thus impaired DNA repair through homologous recombination. Mutations and deletions will be evaluated against the Human Gene Mutation database and other online databases (ClinVar, Breast Cancer Information Core, PubMed) to evaluate the functional relevance, and to make a determination on the likelihood of the mutation resulting in defective homologous recombination-dependent DNA repair. Variants of unknown significance will not be eligible.

Examples of evaluable mutations by commercially available somatic and germline genetic testing include:

Somatic	*RAD50/51/51B, BARD1, BLM, BRCA1, BRCA2, BRIP1, FANCA/C/D2/E/F/G/L, PALB2, or BAP1*
Germline	*RAD50/51/51B, BARD1, BLM, BRCA1, BRCA2, BRIP1, FANCA/C/D2/E/F/G/L, PALB2, or BAP1*

If a pathogenic mutation in the HR pathway is confirmed and not listed above, the study PI will determine if the patient is eligible based on available clinical or pre-clinical literature.

Patients with advanced solid tumor malignancies with documented germline or somatic deleterious mutations involving genes critical to DNA repair through homologous recombination, and who have an adequate performance status (PS), bone marrow, hepatic, and renal function will be screened for enrollment. If a patient is eligible because they have a known deleterious germline mutation, testing must have been performed in a clinical laboratory improvement amendments (CLIA) certified laboratory prior to study entry. Patients who ultimately meet the inclusion and exclusion criteria as detailed in Section 3, and desire participation, will be enrolled. Accrual will rely on physician referral of patients identified as having tumor expression of a deleterious HR mutation who are thought likely to benefit from trial therapy over standard therapies. Similarly, we will rely on physician referrals of patients identified as having a germline deleterious HR mutation. Patients can enroll in the first-line treatment setting, or following any previous non-PARP inhibitor-based therapy(ies) or any previous platinum-based therapy(ies) assuming the last platinum dose was greater than 6 months prior to enrolment (or 12 months for breast cancer patients, see Section 3.3.1) and there was no disease progression while on platinum chemotherapy. Eligible patients who desire enrollment in the first-line setting will require documentation of standard of care therapy refusal.

Patients will be PRE-identified as having the homologous recombination mutations based on NGS done PRIOR to enrollment in this current protocol. The testing may have been done at any time prior to enrollment.

In the Phase Ib portion of study, there will be an expansion cohort of 20 additional patients with similar documented germline or somatic deleterious mutations critical to DNA repair through homologous recombination – and who have biopsiable and measurable disease, and an adequate performance status (PS), bone marrow, hepatic, and renal function. These patients will be treated at the recommended Phase II dose and schedule determine in the Phase Ia portion of the trial.

- For the Phase Ib portion of the trial, if any patient has had NGS testing more than 12 months prior to enrollment then a repeat NGS test must be done and the deleterious mutation identified for inclusion. (Note that this stipulation does not include patients who have confirmation of a deleterious germline mutation. These patients may have been identified at any time point prior to inclusion in the protocol and do NOT need to have this genetic testing repeated regardless of time frame and intervening therapy).

4.1.1 Phase Ia Portion (Dose Escalation Procedures)

During the Phase I Portion of the study, patients will be enrolled in a 3+3 alternating dose escalating fashion to determine the RP2D and schedule of niraparib plus carboplatin, to a maximum dose of niraparib of 300mg daily and a maximum dose of carboplatin AUC of 4. To start, 3 patients will be enrolled at dose level 1, niraparib [redacted] (Table 1, *Schedule #1*). This starting dose is selected to be above the dose level previously identified as leading to significant PARP inhibition (80mg daily dose), but below the current recommended dose of 300mg due to concerns for combined toxicity with platinum therapy. Given concern for adverse events with this combination, particularly myelosuppression, patients will receive the first cycle with niraparib alone, to enable the evaluation of PARP inhibitor therapy alone in each individual patient. Because these patients' tumors harbor defects in homologous recombination, we would anticipate these patients will gain some anti-tumor benefit from the PARP inhibitor therapy alone – alleviating any concerns over compromising efficacy in this niraparib alone run-in cycle.

Then, starting cycle 2, carboplatin will be added. To maximize PARP inhibition prior to dosing with carboplatin, carboplatin will be given on Day 2 of a given cycle. The starting dose of carboplatin in dose level 1 will be AUC [redacted] on day 2 of each 21 day cycle. This starting dose is well below the AUC=5 dose at which significant myelosuppression has previously been observed.

Figure 1: Treatment and Biopsy Schedule: Niraparib ([redacted]

The 3+3 schema will be employed to ensure safety and tolerability. With this design, if there are less than 2 dose-limiting toxicities (DLTs) in the first 3 patients, then 3 additional patients will be enrolled to the current dose level cohort. If there are less than 2 dose-limiting toxicities (DLTs) in these 6 patients, then 3 additional patients will be enrolled in the next dose level (Table 1), and so on. If there are greater than or equal to 2 DLTs in a given 6 patient cohort, then the dose level below will be considered the maximum tolerated dose (MTD) and will be employed as the RP2D and schedule. If dose level 1 is not tolerated, then an alternative schedule will be pursued

(Section 4.1.1.1). The RP2D and schedule will be used for the Phase Ib portion of the study. While 9 dose levels are depicted in Table 1, it is very possible that dose escalation will stop at a dose level <9.

Dose Cohort	Niraparib (mg Daily)	Carboplatin (AUC)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]

Table 1: Dose Escalation for Carboplatin and Niraparib (Niraparib Dosing [redacted])

Patients will be monitored for safety with blood tests, clinic visits, and physical exams weekly for the first 3 cycles, on the first day of the week (e.g. Days 1, 8, and 15). Patients will return for carboplatin dosing on Day 2 beginning with the second cycle, but labs from the previous day will not need to be redrawn. Restaging exams will occur every 9 weeks, as determined by the cycle number and not the calendar. However, if there are any significant delays, restaging exams must not occur more than 12 weeks apart. Patients who have SD at restaging, and who are adequately tolerating therapy will remain on study. For cycles 4 and beyond, patients will have clinic visits, physical exams and lab work on Day 1 only, assuming no toxicities of grade 2 or greater. They will have to return for carboplatin infusion (either Day 2, or days 2 and 9 according to the alternative treatment schedules below). **If a dose change occurs (i.e. alternative schedule pursued), patients will undergo weekly blood tests, clinic visits, and physical exams for 1 cycle, then will undergo evaluations on Day 1 only of each subsequent cycle.** Interim analyses to assess secondary endpoints of OS and PFS will be scheduled to occur at 12 months and 24 months.

In addition to dose-escalation evaluation, pharmacodynamic studies will be evaluated on participant's biopsy samples and serial serum samples, directed towards an assessment of DNA damage including γH2AX and RAD51 foci formation, as well as an assessment of PARP inhibitory activity, as measured by a PARP-trapping assay. We will also undertake NGS analysis of DNA repair enzymes at the time of progression (off study) to evaluate markers that predict response and resistance to therapy. In addition, a portion of all pre-treatment tumor samples will be used in *ex vivo* models (e.g. organoids) for further analysis of mechanism of resistance and to identify combinatorial therapies that can overcome resistance.

4.1.1.1 Alternative Schedules

Given concerns over the potential for combinatorial toxicity, especially on myelosuppression, two alternative dosing schedules will be considered. The decision to pursue one or both of these alternative schedules will be determined by the PIs and will take into account toxicities observed to date, as well as the pharmacodynamic effects observed on serial tumor biopsies.

Thus, for example, if dose level 1 is too toxic in Schedule #1 (i.e. with 2 or more DLTs), then patients will be enrolled according to Schedule #2. If Schedule #2 remains too toxic, then Schedule #3 will be employed.

However, the investigators will also be reviewing the pharmacodynamic assessments of DNA damage, and will have the opportunity to compare these results to the clinical efficacy. If these pharmacodynamics assessments suggest that an alternative schedule may be more efficacious, or that an alternative schedule merits scientific exploration, then the investigators may choose as a group to pursue one or both of the alternative schedules. Ultimately, the schedule and the dose must be selected by the investigators prior to enrollment of the Phase Ib expansion cohort – as patients in the Phase Ib expansion cohort will be enrolled in only one RP2D and schedule.

In the first alternative schedule (*Schedule #2*), niraparib will only be dosed on Days [redacted] of an every 21 day cycle (Figure 2). The dose escalation will be otherwise similar (Table 2). Pre-treatment biopsies will again be obtained, as depicted in Figure 2.

Figure 2: Treatment and Biopsy Schedule: Niraparib (Days [redacted])

Dose Cohort	Niraparib (mg Daily)	Carboplatin (AUC)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]

Table 2: Dose Escalation for Carboplatin and Niraparib (Niraparib Dosing [redacted])

The second alternative schedule (*Schedule #3*) will not include dose-escalation of carboplatin, and as such patients will receive carboplatin AUC [redacted] weekly for 2 weeks on, 1 week off of every q3week cycle (Table 3). In addition, niraparib will only be given [redacted]). Carboplatin will be given on Days 2 and 9 (Figure 3). Pre-treatment biopsies will again be obtained, as depicted in Figure 3.

Figure 3: Treatment and Biopsy Schedule: Weekly Carboplatin

Dose Cohort	Niraparib (mg Daily)
1	[redacted]
2	[redacted]
3	[redacted]

Table 3: Dose Escalation - Weekly Carboplatin

4.1.2 Phase Ib Portion (Dose Expansion Procedures)

Once the recommended dose and schedule–as determined by safety and pharmacodynamic assessment–has been established, an expansion cohort will be planned for 20 patients total. Twenty patients will be enrolled with deleterious DNA repair mutations (as in Phase Ia) to accelerate our understanding of the efficacy of this combination, in preparation for Phase II or III study. We anticipate identifying a higher number of breast cancer patients with HR deficient tumors due to frequent utilization of germline genetic testing. In order to obtain information about this combination in a variety of tumor types, we will cap the number of breast cancer patients at 10 total. Similarly, in order to obtain information in patients with a variety of defects in HR, the total number of patients with *BRCA1/2* mutations (any disease type) will also be capped at 10 total.

Patients will be evaluated with clinic visits, physical exams, and blood tests weekly for the first cycle, then on Day 1 of subsequent cycles only, unless clinically indicated sooner. Restaging images will occur every 9 weeks. If at first restaging there is no evidence of PD, as determined by RECIST v1.1 criteria, and the patient is tolerating therapy, then the patient will continue on study therapy. Patients will continue to remain on study as long as there is no evidence of PD (according to RECIST v1.1 criteria) and the therapy is adequately tolerated. Patients will have a tumor biopsy prior to treatment, a second and third biopsy on treatment based on the schedule chosen in Phase Ia (outlined in Sections 4.1.1 and 4.1.1.1), and a final biopsy at the time of PD for correlative study.

After all 20 patients have undergone their initial response assessment at week 9, an interim analysis will be conducted to determine how many had a PR, CR, SD, or PD. The study will be stopped early if 4 or fewer patients obtain a PR, CR, or SD at 9 weeks. If the study progresses, patients will continue on study therapy with follow up evaluations as previously delineated, assuming no significant associated toxicities, with restaging scans to assess response every 9 weeks. Interim analyses to assess secondary endpoints of OS and PFS will be scheduled to occur at 12 months and 24 months. If patients develop progressive disease, they will be followed from progression until death to assess overall survival.

All patients in the Phase 1b portion will undergo three serial tumor biopsies to assess the pharmacodynamic effects of niraparib, and then niraparib plus carboplatin on DNA repair. An off study/at progression tumor biopsy will also be required. Correlative studies for the serial tumor biopsies will be the same as for the Phase Ia.

Therefore, patients will be required to undergo serial tumor biopsies to assess the effect of niraparib alone, and of niraparib plus carboplatin (Figure 1). Specifically, patients will be required to undergo a second tumor biopsy (niraparib therapy alone) on Cycle 1, Day 14 (range C1D10-14) and a third tumor biopsy (niraparib plus carboplatin) on Cycle 2, Day 14 (range C2D10-14). ***There can be some flexibility with the timing of the biopsies, but it is important that the second and third biopsies take place on a day that the patient received a dose of niraparib.***

All patients whose disease has NOT rapidly progressed on trial will undergo a biopsy upon disease progression for ongoing correlative studies. Specifically, patients who meet the following conditions will have a biopsy upon progression:

The patient experiences a RECIST 1.1 confirmed partial or complete response at any point, and then subsequently experiences disease progression

Or

The patient experiences stable disease of ≥27 weeks (to comport with the timing of restaging imaging), and then subsequently experiences disease progression.

4.2 Patient Screening and Enrollment

Study activities are detailed in Table 4, and a study activity checklist in Table 5. Screening will occur within 14 days prior to administration of the first dose of niraparib. Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken. For procedures performed at screening and repeated, the later procedure performed prior to dosing, will serve as a baseline for clinical assessment. A complete history and physical will be obtained at the screening visit. Additionally, labs will be reviewed/ordered during the screening visit, prior to the initiation of therapy.

Patients who pass screening will again undergo a full evaluation on Cycle 1 Day 1, including a physical examination, vital signs, performance status, chemistry, hematology, medication review, and adverse event evaluation. If any abnormality that would be an exclusion is identified at subject assessment at any time prior to initiating therapy on Cycle 1, Day 1, the patient will not start treatment until the abnormality is resolved, and the patient again meets all inclusion/exclusion criteria.

For patients being considered for enrollment outside of Georgetown-Lombardi, all primary source documentation should be sent to Georgetown University's LCCC Consortium IIT Office and the Principal Investigator, Dr. Isaacs, for review and approval. Patients must be approved for accrual prior to starting study medications. Records should be emailed to Georgetown University's LCCC Consortium IIT Office and Dr. Isaacs to confirm eligibility.

The screening procedures include the following listed below.

4.2.1 Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken.

4.2.2 Medical History

The following information will be collected during the Screening Period:

1) Complete medical history, including documentation of any clinically significant medical conditions
2) History of tobacco and alcohol use
3) Presence and severity of any symptoms/conditions associated with their advanced solid tumor malignancy

4) Detailed oncology history, including:
    a. Date of primary cancer diagnosis
    b. Pathology (histology or cytology) of primary tumor
    c. Metastasis information (including the location)
    d. Surgical history
    e. Anti-cancer and radiation treatments administered (including dates and type of modality, and if therapy was in the neoadjuvant, adjuvant, or metastatic setting)
5) At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded in the CRF. On Cycle 1 Day 1 any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing up through the date of the off study visit

4.2.3 Demographics
Age, gender, race and ethnicity will be recorded.

4.2.4 Review subject eligibility criteria

4.2.5 Review previous and concomitant medications

4.2.6 Physical exam including vital signs, height, and weight
A complete physical examination will be performed at the Screening Visit. Body weight will be recorded during every physical exam. The subject will wear lightweight clothing and no shoes during weighing. Height will be measured at the Screening Visit only; the subject will not wear shoes.

4.2.7 Vital sign determinations
Vital sign determinations of heart rate, blood pressure and body temperature will be obtained at the Screening Visit. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

4.2.8 Performance Status (PS)
PS will be evaluated prior to study entry according to Table 11 in Appendix A.

4.2.9 Hematology
Hematology samples (complete blood count [CBC]) will be collected and assessed using a certified laboratory. The Investigator will review, initial and date all laboratory results. Any laboratory value outside the reference range stated in the inclusion criteria will preclude the patient from study participation.

4.2.10 Serum chemistries
Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. Any laboratory value outside the reference range stated in the inclusion criteria will preclude the patient from study participation.

4.2.11 Pregnancy Test
For female subjects of childbearing potential, a serum or urine pregnancy test will be performed at the Screening Visit within 14 days of Cycle 1 Day 1 and a urine pregnancy test will be done within 72 hours of C1D1 or at the Cycle 1 Day 1 (C1D1) visit prior to the first dose of study drug. Female patients will not be eligible for enrollment if she has a positive urine or serum pregnancy test ≤3 days prior to study drug administration, is breast-feeding, or is planning to conceive children within the projected duration of the study treatment. Subjects considered not of childbearing potential must be documented as being surgically sterile or post-menopausal (for at least 1 year). The test results must be reviewed and determined to be negative prior to dosing. If the urine pregnancy test is positive at Cycle 1 Day 1, it should be confirmed by a serum pregnancy test. The test may be repeated at the discretion of the investigator at any time during the study. Should a female study subject become pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately,

as well as the study PI (Dr. Isaacs) and GSK, as outlined in Section 6.7. If a patient becomes pregnant, or if a patient's spouse becomes pregnant while on trial, he or she will be removed from the study immediately.

4.2.12 Tumor assessment

Subjects must have measurable disease, defined as at least 1 unidimensionally measurable lesion as defined by RECIST v1.1 (tumor ≥ 1 cm in longest diameter on axial image on CT or MRI and/or lymph node(s) ≥ 1.5 cm in short axis on CT or MRI). Subjects must also have tumor tissue amenable to serial biopsies.

4.3 Treatment Assignment and Tumor Assessment

4.3.1 Patient Study Number Assignment and Sample Labeling

A scientific objective of this Phase I study is to assess the pharmacodynamic effects of niraparib in addition to carboplatin on tumor tissue and to correlate those effects with efficacy measures. Thus, for all patients, a pre-treatment biopsy will be required. In addition, for all patients in the Phase Ib portion, we will require 4 core biopsies of a primary tumor or metastatic lesion:

- A fresh core biopsy prior to treatment (within 4 weeks of Cycle 1 Day 1)
- A repeat core biopsy on Cycle 1 Day 14 (range C1D10-14), preferably on the same tumor site if possible
- A repeat core biopsy on Cycle 2 Day 14 (range C2D10-14), preferably on the same tumor site if possible
- A final core biopsy after PD or off study, preferably on the same tumor site if possible, with the same specifications as listed above in section 4.1.1.

This biopsy scheduling schema will differ if alternative schedules pursued, and will be updated as needed by the PIs.

- For the Phase Ib portion, NGS does not need to be repeated on the pre-treatment biopsy sample, if a patient's initial NGS was completed within 12 months of enrollment. HOWEVER, if any patient has had NGS testing more than 12 months prior to enrollment then a repeat NGS test must be done and the deleterious somatic mutation must be re-identified for inclusion. (Note that this stipulation does not include patients who have confirmation of a deleterious germline mutation. These patients may have been identified at any time point prior to inclusion in the protocol and do NOT need to have this genetic testing repeated regardless of time frame and intervening therapy).

The specific procedures of biopsy collection are outlined below in Section 4.3.2. Throughout the study, the following labeling procedures will be followed.

4.3.1.1 Patient Sample Labeling

Patients will be de-identified and labeled with a 12 character study label (XX-X-X-XXXXXX):

- The first two characters will be the patient's initials
- The third character will be the site number from which the patient was enrolled (single digit)
    - 1 = Georgetown
    - 2 = Yale
    - 3 = Hackensack
    - 4 = Levine
    - 5 = John's Hopkins
    - 6 = Vanderbilt
    - 7 = Other
- The fourth and fifth characters will be the patient study number (e.g. 01, 02, 03, etc.)
- The sixth character will be the timing of collection
    - 1 = First biopsy/sample
    - 2 = Second biopsy/sample
    - 3 = Third biopsy/sample
    - 4 = Fourth biopsy/sample at Final Off Study Visit or at progression
    - 5 = Serum collection
- The final characters will be the date in MM/DD/YR format

4.3.2 Tumor Biopsy Algorithm (Please See the Corresponding Lab Manual)

A rigorous tumor collection algorithm will be instituted for this protocol. Shipping details and addresses are all summarized in Appendix D. If alternative treatment schedules pursued, the timing of tissue biopsies will differ from what is outlined below, and the schedule will be updated by a PI as needed.

Of note, patients who are on chronic anticoagulation will be required to hold anticoagulation prior to the biopsies being performed. Patients on warfarin must hold treatment for 5 days, but will be on low molecular weight heparin (LMWH), 1 mg/kg subcutaneously twice a day. The LMWH will continue until the last biopsy is complete. Patients may then resume warfarin the day after the last biopsy. Additionally, patients on LMWH will hold (i.e., not receive) the dose of LMWH the morning of the procedure, but will resume the LMWH the evening of the day of the biopsy.

4.3.2.1 Timing of the Pre-Treatment Biopsy

Following successful screening and enrollment of patients with an advanced solid tumor malignancy and known deleterious mutations in selected DNA repair genes, a pre-treatment tumor biopsy will be obtained (within 4 weeks of Day 1 of study treatment).

- For the Phase Ib portion, NGS does not need to be repeated on the pre-treatment biopsy sample, if a patient's initial NGS was completed within 12 months of enrollment. HOWEVER, if any patient has had NGS testing more than 12 months prior to enrollment then a repeat NGS test must be done and the deleterious somatic mutation must be re-identified for inclusion. (Note that this stipulation does not include patients who have confirmation of a deleterious germline mutation. These patients may have been identified at any time point prior to inclusion in the protocol and do NOT need to have this genetic testing repeated regardless of time frame and intervening therapy).

4.3.2.2 Pre-Treatment Biopsy Tissue Utilization and Prioritization

First Biopsy Tissue Utilization and Prioritization

For the first biopsy, 5 individual cores will be obtained with an 18-20 gauge needle. Any extra cores that are taken, and are not needed will be embedded in paraffin, and the formalin-fixed, paraffin embedded (FFPE) block(s) will be kept in the lab of Dr. Brody. The cores will be prepared as follows:

- The first two cores will be placed in an institution-supplied single formalin vial, and sent to Dr. Brody's lab at OSHU for testing.
- The next two cores (*ex vivo* samples) will be placed in a pre-provided single Eppendorf tube with collection media. This will be shipped on ice to Dr. Brody's lab at OSHU.
- The last core will be placed in a pre-supplied single formal vial from the Caris Life Sciences collection kit and sent to Caris for NGS testing

4.3.2.3 Second Biopsy – Cycle 1 Day 14 *(For patients in the Phase Ib portion)*

A second biopsy will be obtained as outlined in Figures 1-3 following 14 (range 10-14) days of therapy with niraparib to assess the tumor effect of therapy with niraparib alone. The second biopsy will occur on C1D14 (range C1D10-14). If unable to perform biopsy within this timeframe (weekend, holiday), biopsy planning will have to be reviewed on a case-by-case basis with a study PI (Dr. Isaacs). There can be some flexibility with the timing of the biopsies, but it is important that the second biopsy takes place on a day that the patient received a dose of niraparib. The second biopsy will be used for serial pharmacodynamic tests identical to those evaluated with the first biopsy sample.

4.3.2.4 Second Biopsy Tissue Utilization and Prioritization *(For patients in the Phase Ib portion)*

Second Biopsy Tissue Utilization and Prioritization

For the second biopsy, 5 individual cores will be obtained with an 18-20 gauge needle. Any extra cores that are taken, and are not needed will be embedded in paraffin, and the FFPE block(s) will be kept in the lab of Dr. Brody. The cores will be prepared as follows:

- The first three cores will be placed in an institution-supplied single formalin vial, and sent to Dr. Brody's lab at OHSU for testing.
- The last two cores (*ex vivo* samples) will be placed in a pre-provided single Eppendorf tube with collection media. This will be shipped on ice to Dr. Brody's lab at OHSU.

4.3.2.5 Third Biopsy – Cycle 2 Day 14 *(For patients in the Phase Ib portion)*

A third biopsy will be obtained as outlined in Figures 1-3 following initiation of cycle 2 to assess the tumor effect of therapy with carboplatin in addition to niraparib. The second biopsy will occur on C2D14 (range C2D10-14).

If unable to perform biopsy within this timeframe (weekend, holiday), biopsy planning will have to be reviewed on a case-by-case basis with a study PI (Dr. Isaacs). There can be some flexibility with the timing of the biopsies, but it is important that the third biopsy takes place on a day that the patient received a dose of niraparib. The third biopsy will be used for serial pharmacodynamic tests identical to those evaluated with the first biopsy sample.

4.3.2.6 Third Biopsy Tissue Utilization and Prioritization *(For patients in the Phase Ib portion)*
Third Biopsy Tissue Utilization and Prioritization
For the third biopsy, 5 individual cores will be obtained with an 18-20 gauge needle. Any extra cores that are taken, and are not needed will be embedded in paraffin, and the FFPE block(s) will be kept in the lab of Dr. Brody. The cores will be prepared as follows:

- The first three cores will be placed in an institution-supplied single formalin vial, and sent to Dr. Brody's lab at OHSU for testing.
- The last two cores (ex vivo samples) will be placed in a single pre-provided Eppendorf tube with collection media. This will be shipped on ice to Dr. Brody's lab at OHSU.

4.3.2.7 Biopsy Upon Progression *(For patients in the Phase Ib portion)*
All patients whose disease has NOT rapidly progressed on trial will undergo a biopsy upon disease progression for ongoing correlative studies. Specifically, patients who meet the following conditions will have a biopsy upon progression:

- The patient experiences a RECIST 1.1 confirmed partial or complete response at any point, and then subsequently experiences disease progression
  Or
- The patient experiences stable disease of ≥27 weeks (to comport with the timing of restaging imaging), and then subsequently experiences disease progression

The final biopsy will be used for serial pharmacodynamic tests identical to those evaluated with the first biopsy sample, as well as NGS testing.

4.3.2.8 Biopsy Upon Progression Tissue Utilization and Prioritization *(For patients in the Phase Ib portion)*
Biopsy Upon Progression Tissue Utilization and Prioritization
For the fourth biopsy, 5 individual cores will be obtained with an 18-20 gauge needle. Any extra cores that are taken, and are not needed will be embedded in paraffin, and the FFPE block(s) will be kept in the lab of Dr. Brody. The cores will be prepared as follows:

- The first two cores will be placed in an institution-supplied single formalin vial, and sent to Dr. Brody's lab at OHSU for testing.
- The second two cores (ex vivo sample) will be placed in a single pre-provided Eppendorf tube with collection media. This will be shipped on ice to Dr. Brody's lab at OHSU
- The final core will be placed in a pre-supplied single formalin vial, and placed in a shipment kit to be sent to Caris Life Sciences. Caris Life Sciences will perform a 600 gene NGS cancer related exome analysis.

4.3.3 Additional Exploratory Correlative Analyses
During the course therapy, patients will also undergo sample collection for additional correlative analyses:

- Patients will submit a 10mL sample of blood in a red top tube for future research on Cycle 1 Day 1 and every 3 weeks until progression. These samples will be processed to isolate serum and stored frozen until shipped. Samples will be batched and shipped frozen to Dr. Brody's lab at OHSU.

4.4 Detailed Patient Assessments
4.4.1 Patient Monitoring Until Progression
Subject assessments (physical examinations, vital signs, performance status, laboratories, medication review, and adverse event evaluations) will be conducted at screening, Cycle 1 Day 1, every week for cycles 1-3 (on the first day of the week – D8, for example), and then on Day 1 only of subsequent cycles, assuming patient has achieved SD, PR, or CR. Study visits may be performed 3 days before or after the scheduled date due to unforeseen or unavoidable circumstances, and attempts should be made to schedule visits to line up with the start of a new cycle (within the constraints of the above parameters). Study drugs will be dispensed at the last visit prior to the start of the next 21 day cycle. The radiologic first response assessment at 9 weeks, and subsequent radiologic response assessments every 9 weeks thereafter, may be performed up to 7 days before

or after the scheduled date due to unforeseen or unavoidable circumstances. Details are provided in Table 4, and a checklist highlighting the important events for screening through the completion of the trial is provided below, as Table 5.

Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and for procedures performed at screening and repeated, the later procedure performed prior to dosing will serve as a baseline for clinical assessment. If any abnormality that would be an exclusion is identified at subject assessment at any time prior to initiating therapy on Day 1, the patient will not start treatment until the abnormality is resolved, and the patient again meets all inclusion/exclusion criteria. The monitoring procedures include the following listed below.

4.4.1.1 Medical History

At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded in the CRF. On Cycle 1 Day 1 any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing up through the date of the off study visit.

4.4.1.2 Physical Examinations

A physical examination including height, weight, vital signs, and performance status will be performed weekly for cycles 1-3. Patients with SD, PR, or CR at restaging after cycle 3 will have clinic visits and physical exams Day 1 only. Any significant physical examination findings after the administration of the first doses of niraparib and carboplatin will be recorded as adverse events. Body weight will be recorded during every physical exam. The subject will wear lightweight clothing and no shoes during weighing. Weight will be measured on the same scale at each visit. Height will be measured at the screening visit only; the subject will not wear shoes.

4.4.1.3 Vital Signs

Vital sign determinations of body temperature (in degrees Celsius), heart rate, respiratory rate, and blood pressure will be obtained at the screening visit, on each day the subject is seen by the treating physician, and at the final visit. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

4.4.1.4 Clinical Laboratory Tests

All subjects will undergo the laboratory assessments outlined in Table 4.

1. A CBC with differential will be collected at the screening visit, on Cycle 1 Day 1, weekly through the first 3 cycles, and then on Day 1 only thereafter (unless clinically indicated sooner) for Phase Ia. For Phase Ib, a CBC with differential will be collected at the screening visit, on Cycle 1 Day 1, weekly through the first cycle, and then on Day 1 only thereafter (unless clinically indicated sooner).
2. Serum chemistries (total protein, albumin, total bilirubin, AST, ALT, ALP, sodium, potassium, chloride, bicarbonate, BUN, creatinine, and calcium) will be collected at the screening visit, on Cycle 1 Day 1, weekly through the first 3 cycles, and then on Day 1 only thereafter (unless clinically indicated sooner) for Phase Ia. For Phase Ib, serum chemistries (total protein, albumin, total bilirubin, AST, ALT, ALP, sodium, potassium, chloride, bicarbonate, BUN, creatinine, and calcium) will be collected at the screening visit, on Cycle 1 Day 1, weekly through the first cycle, and then on Day 1 only thereafter (unless clinically indicated sooner).
3. PT/PTT/INR will be collected at the screening visit, on Cycle 1 Day 1, and on Cycle 2, Day 1, and at the final visit.

Laboratory samples for this study will be assessed using the certified laboratory at the investigators' institutions or at a clinical laboratory such as Quest or LabCorp and these data will be used for all data analysis. The Principal Investigator or sub-investigator will review, initial and date all laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 6.3.

4.4.1.5 Tumor Imaging Assessment

Baseline imaging should be performed within four weeks of initiating therapy. Ideally, this will included a CT scan of the chest, abdomen, and pelvis with oral and IV contrast, or can consist of an abdominal MRI and positron emission tomography (PET) scan for patients who cannot undergo a contrast-enhanced CT scan. If a patient has an allergy to IV contrast, appropriate pre-medication can be given to prevent a contrast reaction. Patients may undergo other modalities such as an MRI instead of a CT scan at the treating physician's discretion if appropriate (such as severe allergy to CT contrast, extremity tumors, bone metastases requiring bone scans, etc.). Patients must have measurable disease as per RECIST v1.1 and the index lesions could not have been previously treated with local therapy, such as radiation.

4.4.1.6 Timing of Assessments

Treatment will be initiated on Cycle 1 Day 1, and patients will be evaluated every week during the first 3 cycles for Phase Ia and every week during the first cycle for Phase Ib, and then on Day 1 only of subsequent cycles, as outlined above. To be clear, for the purposes of standardizing data collection, patient data (blood test results, H&P results, etc) will be collected at "protocol defined visits." These visits may or may not coincide with the regular visits that a physician may wish to have with the patient, but these will be required visits used for data collection. Restaging exams will occur every 9 weeks, as determined by the cycle and not the calendar in both the Phase Ia and Phase Ib portion of study. If there are any significant delays, restaging exams must not occur more than 12 weeks apart. During the treatment period, a visit window of +/- 2 days will be allowed.

4.4.1.7 Adverse event assessment

Baseline symptoms at Cycle 1 Day 1 (prior to initiating therapy) should be detailed and graded. Once treatment has started, adverse events will be assessed weekly through the end of cycle 3 at the protocol defined visits. Beginning with cycle 4, adverse events will be assessed every three weeks on Day 1 of each subsequent cycle. The individual investigator should record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. See Section 6.5 for Adverse Event monitoring and reporting. The Principal Investigator or sub-investigators will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 5.0.
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All adverse events will be followed to a satisfactory conclusion.

4.4.1.8 Correlative Blood Samples and Patient-Reported Outcomes

Correlative blood samples and patient-related outcomes surveys will be obtained at time frames detailed below in Section 9.

4.4.1.9 Unscheduled Assessments

For any suspected myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) case reported while a patient is receiving treatment or followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the study site receives a copy of the hematologist's report, which must include a classification according to World Health Organization (WHO) criteria[108]. The site must keep a copy of the report with the patient's study file.

4.4.2 Response Assessment

Patients will receive therapy until disease progression, as per RECIST v1.1, or therapy intolerance. Dose and schedule modifications will depend upon the specific regimen selected. Response assessment will occur every 9 weeks (+/- 7 days), based on the cycle. If there are any significant delays, restaging exams must not occur more than 12 weeks apart. Only patients with SD, PD, or CR, as demonstrated by RECIST v1.1 will continue on treatment per protocol.

Response assessment will continue every 9 weeks, and patients will continue to receive therapy, with dose adjustments if necessary, as detailed below until disease progression per RECIST v1.1 or treatment intolerability.

4.4.3 Removal of Subjects from Study

Each subject has the right to withdraw from study treatment at any time. In addition, the investigator may discontinue a subject from the study treatment at any time for any reason if the investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol. Each subject will be withdrawn from the study if any of the following occur:

1) The subject experiences either clinical or radiographic progressive disease.
2) The subject requires radiotherapy or alternate antineoplastic agents during the study period.
3) The investigator believes it is in the best interest of the subject.
4) Clinically significant deterioration of the subject's medical status as determined by the investigator.
5) The subject requires alternative anti-cancer agents or non-palliative radiation therapy for primary or metastatic disease during the treatment portion of the study.
6) Subject becomes pregnant or begins breastfeeding during the treatment portion of the study.
7) The subject or subject's legally acceptable representative decides to withdraw consent for any reason.
8) Any other medical reason that the study investigator deems appropriate.

4.4.3.1 Discontinuation of Individual Subjects

When a subject discontinues from the study (without reaching a protocol-defined endpoint), the investigator will notify the principal investigator as soon as possible (provided, in each case, subject care and safety are not compromised). When a subject discontinues the study, a final visit will be conducted, preferably prior to the initiation of another anticancer therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the investigator's best clinical judgment. At the final visit, the reason(s) for the discontinuation from the study will be recorded and a physical examination, body weight, vital signs measurement, laboratory analyses, performance status, tumor assessment, collection of unused study drug and an assessment of adverse events will be performed as soon as possible after discontinuation from the study. If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved. In the event that a positive result is obtained on a pregnancy test for a subject during the study, the administration of study drug to that subject must be discontinued immediately. Response assessment must be done at the end of treatment visit, if not done within 30 days prior.

4.4.3.2 Patient Replacement Criteria

In the event a patient is removed from the study due to reasons other than disease progression, severe adverse side effects related to the study drug, or patient death (situations in which outcomes will be considered evaluable), then an additional patient will be enrolled as needed to meet protocol accruement goals. For patients who are removed from the study prior to completion of greater than or equal to 14 days of niraparib, additional patients will be enrolled as needed to meet protocol accruement goals.

4.4.3.3 Discontinuation of Entire Study

The investigators may terminate this study provided that written notice is submitted at a reasonable time in advance of the intended termination. The following procedures for discontinuation will be followed:

1) If the investigators have decided to prematurely discontinue the study, the investigators will promptly notify in writing the IRB of the decision and give detailed reasons for the discontinuation.
2) The principal investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of protocol therapy, if applicable, by other appropriate regimens.

4.4.4 Longitudinal Outcomes Assessment

Patients will be followed after progression until death (or up to 24 months) to assess overall survival, and to monitor for the development of secondary malignancies. Information pertaining to survival and post-treatment therapy will be collected approximately every 12 weeks (Month 3, 6, 9, 12, 15 and 18) beginning after the final visit, for a period up to 24 months.

4.4.5 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects.

Table 4a: Study Activities for Phase Ia, Schedule #1

ASSESSMENT/EVENT	Screening ≤28 Days prior to C1D1	≤14 Days prior to C1D1[17]	Treatment Period[16]													Every 9 weeks	EOT	Follow Up
			Cycle 1			Cycle 2				Cycle 3				Cycle 4 >				
			C1D1	C1D8	C1D15	C2D1	C2D2	C2D8	C2D15	C3D1	C3D2	C3D8	C3D15	D1	D2			
Administrative procedures and forms																		
Informed consent	X[18]																	
Medical History & Demographics	X																	
Eligibility Criteria Inclusion/Exclusion Patient Registration[1]	X																	
ECOG PS	X	X	X	X	X	X		X	X	X		X	X	X			X	
Concomitant Medications Collection	X	X	X	X	X	X		X	X	X		X	X	X		X	X	
Adverse Events Assessments[2]			X	X	X	X		X	X	X		X	X	X		X	X	
Long-term follow up including survival and secondary malignancy																		X[14]
Procedures and tests																		
Physical Examination	X	X	X	X	X	X		X	X	X		X	X	X		X	X	
Vital Signs, Height[3], Weight (temperature, pulse, respiratory rate, and blood pressure)	X	X	X	X	X	X		X	X	X		X	X	X		X	X	
Tumor Biopsy[8]	X																	
Imaging Assessments																		
RECIST Criteria - Tumor evaluation and assessment	X															X	X[15]	
CT Scan	X[4]															X	X[15]	
MRI Scan	X[4]															X	X[15]	
Laboratory Assessments																		
Hematology (CBC w/ diff and platelets)	X	X	X	X	X	X		X	X	X		X	X	X		X	X	

Coagulation: Prothrombin Time (PT) and INR; Activated Partial Thromboplastin Time (aPTT)[5]	X																		
Serum Chemistries[6]	X	X	X	X	X	X		X	X	X		X	X	X		X	X		
Pregnancy test[7]		X	X			X				X				X					
Research Serum Samples[9]			X			X				X				X			X		
Caris NGS testing	X[10]																		X[11]
Drug Administration																			
Carboplatin Administration							X				X				X				
Niraparib Dispensing for Oral Administration [redacted]			X			X				X				X					
Study Drug Accountability[13]			X			X				X				X					

1. Patient registration form will be provided. Please ensure all reports required for registration including Pathology Report, Physicians Note validating Previous treatments, Imaging showing RECIST criteria, Laboratory Results and, Past Medical History are de-identified.
2. Adverse Events must be monitored for 30 days post EOT and until resolution to baseline.
3. Height only needs to be captured in Screening.
4. Screening scans are to be performed within 28 days of Cycle 1 Day 1. Tumor measurements evaluated by RECIST 1.1. CTs or MRIs are acceptable.
5. PT/PTT as required for biopsy will be performed at screening.
6. Serum Chemistries include: albumin, ALP, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium total protein, AST, ALT, and sodium.
7. Serum or Urine pregnancy test for women of child-bearing potential, within 14 days of first dose for screening, and repeated within 72 hours of first dose.
8. Tumor biopsy to be performed prior to Cycle 1, Day 1.
9. Research Serum Samples are to be performed at Day 1 of every cycle and at the time of the first radiologic response assessment.
10. NGS does not need to be repeated on the pre-treatment biopsy sample
11. NGS at End of Treatment upon progression is not mandatory.
12. Niraparib will be dispensed on Day 1 of every cycle.
13. Study drug accountability will be performed at Day 1 of every cycle.
14. Patients will be contacted every three months (for 24 months post End of Treatment visit) to collect overall survival and development of secondary malignancy.
15. Imaging must be done at End of Treatment, if not done within 30 days prior.
16. Visit Window during the Treatment period will be +/- 2 days.
17. Assessments done outside of 14 days prior to C1D1 must be repeated within 14 days through prior to treatment on Day 1 to confirm the subject is still eligible.
18. Re-consent is not required if the subject requires re-screening after 28 days, unless there is an updated consent form that requires the subject be re-consented.

Table 4b: Study Activities for Phase Ia, Schedule #2

ASSESSMENT/EVENT	Screening ≤28 Days prior to C1D1	≤14 Days prior to C1D1[17]	Treatment Period[16]													Every 9 weeks	EOT	Follow Up
			Cycle 1			Cycle 2				Cycle 3				Cycle 4 >				
			C1D1	C1D8	C1D15	C2D1	C2D2	C2D8	C2D15	C3D1	C3D2	C3D8	C3D15	D1	D2			
Administrative procedures and forms																		
Informed consent	X[18]																	
Medical History Demographics	X																	
Eligibility Criteria Inclusion/Exclusion Patient Registration[1]	X																	
ECOG PS	X	X	X	X	X	X		X	X	X		X	X	X		X	X	
Concomitant Medications Collection	X	X	X	X	X	X		X	X	X		X	X	X		X	X	
Adverse Events Assessments[2]			X	X	X	X		X	X	X		X	X	X		X	X	
Long-term follow up including survival and secondary malignancy																		X[14]
Procedures and tests																		
Physical Examination	X	X	X	X	X	X		X	X	X		X	X	X		X	X	
Vital Signs, Height[3], Weight (temperature, pulse, respiratory rate, and blood pressure)	X	X	X	X	X	X		X	X	X		X	X	X		X	X	
Tumor Biopsy[8]	X																	
Imaging Assessments																		
RECIST Criteria - Tumor evaluation and assessment	X															X	X[15]	
CT Scan	X[4]															X	X[15]	
MRI Scan	X[4]															X	X[15]	
Laboratory Assessments																		
Hematology (CBC w/ diff and platelets)	X	X	X	X	X	X		X	X	X		X	X	X		X	X	

Coagulation: Prothrombin Time (PT) and INR; Activated Partial Thromboplastin Time (aPTT)[5]	X																	
Serum Chemistries[6]	X	X	X	X	X	X		X	X	X		X	X	X		X	X	
Pregnancy test[7]		X	X			X				X				X				
Research Serum Samples[9]			X			X				X				X			X	
Caris NGS testing	X[10]																	X[11]
Drug Administration																		
Carboplatin Administration							X				X				X			
Niraparib Dispensing for Oral Administration [redacted]			X			X				X				X				
Study Drug Accountability[13]			X			X				X				X				

1. Patient registration form will be provided. Please ensure all reports required for registration including Pathology Report, Physicians Note validating Previous treatments, CT showing RECIST criteria, Laboratory Results and, Past Medical History are de-identified.
2. Adverse Events must be monitored for 30 days post EOT and until resolution to baseline.
3. Height only needs to be captured in Screening.
4. Screening scans are to be performed within 28 days of Cycle 1 Day 1. Tumor measurements evaluated by RECIST 1.1 CTs or MRIs are acceptable.
5. PT/PTT as required for biopsy will be performed at screening.
6. Serum Chemistries include: albumin, ALP, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium total protein, AST, ALT, and sodium.
7. Serum or Urine pregnancy test for women of child-bearing potential, within 14 days of first dose for screening, and repeated within 72 hours of first dose.
8. Tumor biopsy to be performed prior to Cycle 1, Day 1.
9. Research Serum Samples are to be performed at Day 1 of every cycle and at the time of the first radiologic response assessment.
10. NGS does not need to be repeated on the pre-treatment biopsy sample
11. NGS at End of Treatment upon progression is not mandatory.
12. Niraparib will be dispensed on Day 1 of every cycle.
13. Study drug accountability will be performed at Day 1 of every cycle.
14. Patients will be contacted every three months (for 24 months post End of Treatment visit) to collect overall survival and development of secondary malignancy.
15. Imaging must be done at End of Treatment, if not done within 30 days prior.
16. Visit Window during the Treatment period will be +/- 2 days.
17. Assessments done outside of 14 days prior to C1D1 must be repeated within 14 days through prior to treatment on Day 1 to confirm the subject is still eligible.
18. Re-consent is not required if the subject requires re-screening after 28 days, unless there is an updated consent form that requires the subject be re-consented.

Table 4c: Study Activities for Phase Ia, Schedule #3

ASSESSMENT/ EVENT	Screening ≤28 Days prior to C1D1	≤14 Days prior to C1D1[17]	Treatment Period[16]																	EOT	Follow Up
			Cycle 1			Cycle 2					Cycle 3					Cycle 4 >			Every 9 weeks		
			C1 D1	C1 D8	C1 D15	C2 D1	C2 D2	C2 D8	C2 D9	C2D 15	C3 D1	C3 D2	C3 D8	C3 D9	C2D 15	D1	D2	D9			
Administrative procedures and forms																					
Informed consent	X[18]																				
Medical History Demographics	X																				
Eligibility Criteria Inclusion/Exclusion Patient Registration[1]	X																				
ECOG PS	X	X	X	X	X	X		X		X	X		X		X	X			X	X	
Concomitant Medications Collection	X	X	X	X	X	X		X		X	X		X		X	X			X	X	
Adverse Events Assessments[2]			X	X	X	X		X		X	X		X		X	X			X	X	
Long-term follow up including survival and secondary malignancy																					X[14]
Procedures and tests																					
Physical Examination	X	X	X	X	X	X		X		X	X		X		X	X			X	X	
Vital Signs, Height[3], Weight (temperature, pulse, respiratory rate, and blood pressure)	X	X	X	X	X	X		X		X	X		X		X	X			X	X	
Tumor Biopsy[8]	X																				
Imaging Assessments																					
RECIST Criteria - Tumor evaluation and assessment	X																		X	X[15]	
CT Scan	X[4]																		X	X[15]	
MRI Scan	X[4]																		X	X[15]	
Laboratory Assessments																					
Hematology (CBC w/ diff and platelets)(Central Lab)	X	X	X	X	X	X		X		X	X		X		X	X			X	X	

Coagulation: Prothrombin Time (PT) and INR; Activated Partial Thromboplastin Time (aPTT)[5]	X																					
Serum Chemistries[6]	X	X	X	X	X	X		X		X	X		X		X	X			X	X		
Pregnancy test[7]		X	X			X					X					X						
Research Serum Samples[9]			X			X					X					X				X		
Caris NGS testing	X[10]																					X[11]
Drug Administration																						
Carboplatin Administration							X		X			X		X			X	X				
Niraparib Dispensing for Oral Administration Schedule [redacted]			X			X					X					X						
Study Drug Accountability[13]			X			X					X					X						

1. Patient registration form will be provided. Please ensure all reports required for registration including Pathology Report, Physicians Note validating Previous treatments, CT showing RECIST criteria, Laboratory Results and, Past Medical History are de-identified.
2. Adverse Events must be monitored for 30 days post EOT and until resolution to baseline.
3. Height only needs to be captured in Screening.
4. Screening scans are to be performed within 28 days of Cycle 1 Day 1. Tumor measurements evaluated by RECIST 1.1. CTs or MRIs are acceptable.
5. PT/PTT as required for biopsy will be performed at screening.
6. Serum Chemistries include: albumin, ALP, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium total protein, AST, ALT, and sodium.
7. Serum or Urine pregnancy test for women of child-bearing potential, within 14 days of first dose for screening, and repeated within 72 hours of first dose.
8. Tumor biopsy to be performed prior to Cycle 1, Day 1.
9. Research Serum Samples are to be performed at Day 1 of every cycle and at the time of the first radiologic response assessment.
10. NGS does not need to be repeated on the pre-treatment biopsy sample.
11. NGS at End of Treatment upon progression is not mandatory.
12. Niraparib will be dispensed on Day 1 of every cycle.
13. Study drug accountability will be performed at Day 1 of every cycle.
14. Patients will be contacted every three months (for 24 months post End of Treatment visit) to collect overall survival and development of secondary malignancy.
15. Imaging must be done at End of Treatment, if not done within 30 days prior.
16. Visit Window during the Treatment period will be +/- 2 days.
17. Assessments done outside of 14 days prior to C1D1 must be repeated within 14 days through prior to treatment on Day 1 to confirm the subject is still eligible.
18. Re-consent is not required if the subject requires re-screening after 28 days, unless there is an updated consent form that requires the subject be re-consented.

Table 4d: Study Activities for Phase Ib

ASSESSMENT/EVENT	Screening ≤28 Days prior to C1D1	≤14 Days prior to C1D1[17]	Treatment Period[16]														EOT	Follow Up
			Cycle 1			Cycle 2				Cycle 3				Cycle 4 >		Every 9 weeks		
			C1D1	C1D8	C1D15	C2D1	C2D2	C2D8	C2D15	C3D1	C3D2	C3D8	C3D15	D1	D2			
Administrative procedures and forms																		
Informed consent	X[18]																	
Medical History & Demographics	X																	
Eligibility Criteria Inclusion/Exclusion Patient Registration[1]	X																	
ECOG PS	X	X	X	X	X	X				X				X			X	
Concomitant Medications Collection	X	X	X	X	X	X				X				X		X	X	
Adverse Events Assessments[2]			X	X	X	X				X				X		X	X	
Long-term follow up including survival and secondary malignancy																		X[14]
Procedures and tests																		
Physical Examination	X	X	X	X	X	X				X				X		X	X	
Vital Signs, Height[3], Weight (temperature, pulse, respiratory rate, and blood pressure)	X	X	X	X	X	X				X				X		X	X	
Tumor Biopsy[8]	X				X				X								X	
Imaging Assessments																		
RECIST Criteria - Tumor evaluation and assessment	X															X	X[15]	
CT Scan	X[4]															X	X[15]	
MRI Scan	X[4]															X	X[15]	
Laboratory Assessments																		
Hematology (CBC w/ diff and platelets)	X	X	X	X	X	X				X				X		X	X	

Coagulation: Prothrombin Time (PT) and INR; Activated Partial Thromboplastin Time (aPTT)[5]	X		X			X											X		
Serum Chemistries[6]	X	X	X	X	X	X				X				X		X	X		
Pregnancy test[7]		X	X			X				X				X					
Research Serum Samples[9]			X			X				X				X			X		
Caris NGS testing	X[10]																	X[11]	
Drug Administration																			
Carboplatin Administration							X				X				X				
Niraparib Dispensing for Oral Administration [redacted]			X			X				X				X					
Study Drug Accountability[13]			X			X				X				X					

1. Patient registration form will be provided. Please ensure all reports required for registration including Pathology Report, Physicians Note validating Previous treatments, CT showing RECIST criteria, Laboratory Results and, Past Medical History are de-identified.
2. Adverse Events must be monitored for 30 days post EOT and until resolution to baseline.
3. Height only needs to be captured in Screening.
4. Screening scans are to be performed within 28 days of Cycle 1 Day 1. Tumor measurements evaluated by RECIST 1.1. CTs or MRIs are acceptable.
5. PT/PTT as required for biopsy will be performed at screening, on Cycle 1, Day 1, Cycle 2, Day 1, and at the EOT visit.
6. Serum Chemistries include: albumin, ALP, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium total protein, AST, ALT, and sodium.
7. Serum or Urine pregnancy test for women of child-bearing potential, within 14 days of first dose for screening, and repeated within 72 hours of first dose.
8. Tumor biopsy scheduled is dependent upon the final schedule chosen before moving on to Phase Ib. For example, the biopsies may be performed prior to Cycle 1, Day 1; on Cycle 1, Day 14 (range C1D10-14); and on Cycle 2, Day 14 (range C2D10-14), and upon progression (if appropriate, as per Section 4.1.1).
9. Research Serum Samples are to be performed at Day 1 of every cycle and at the time of the first radiologic response assessment.
10. NGS does not need to be repeated on the pre-treatment biopsy sample, if a patient's initial NGS was completed within 12 months of enrollment.
11. NGS at End of Treatment is upon progression.
12. Niraparib will be dispensed on Day 1 of every cycle.
13. Study drug accountability will be performed at Day 1 of every cycle.
14. Patients will be contacted every three months (for 24 months post End of Treatment visit) to collect overall survival and development of secondary malignancy.
15. Imaging must be done at End of Treatment, if not done within 30 days prior.
16. Visit Window during the Treatment period will be +/- 2 days.
17. Assessments done outside of 14 days prior to C1D1 must be repeated within 14 days through prior to treatment on Day 1 to confirm the subject is still eligible.
18. Re-consent is not required if the subject requires re-screening after 28 days, unless there is an updated consent form that requires the subject be re-consented.

Table 5a: Study Activities Checklist for Phase Ia, Schedule #1

Screening (within 4 weeks of Cycle 1, Day 1)

Subject Assessment
Eligibility Criteria
Informed Consent
Demographics
Medical History
Concurrent Medications
Vital Signs
Height
Weight
History and Physical
Performance Status
CBC with Differential
Serum Chemistries
PT/INR, PTT
Caris Molecular Profile with DNA Repair Gene Mutation
Radiology Evaluation and Tumor Measurements
Tumor Amenable to Biopsy
Pre-Treatment Biopsy (1) Scheduled/Complete

Within 2 Weeks of Cycle 1, Day 1

Concurrent Medications
History and Physical
Vital Signs
Weight
Performance Status
CBC with Differential
Serum Chemistries
Pregnancy Test (within 14 days)

Cycle 1, Day 1

Subject Assessment
Concurrent Medications
Pregnancy Test (within 72 hours)
Weight
Vital Signs
History and Physical
Performance Status
Adverse Event Evaluation
CBC with Differential
Serum Chemistries
Research Serum Sample
Dispense Niraparib ([redacted]

Every Week Until First Response Assessment

Subject Assessment
Weight
Vital Signs
Concurrent Medications
History and Physical
Performance Status
Adverse Event Evaluation
CBC with Differential
Serum Chemistries

Cycle 2, Day 1 (In addition to the above)
Research Serum Sample _____
Study Drug Accountability _____
Dispense Niraparib (D1-14) _____
Pregnancy Test _____

Day 2 of Cycles 2 and 3
Carboplatin treatment _____

Cycle 3, Day 1 (In addition to the above)
Research Serum Sample _____
Study Drug Accountability _____
Dispense Niraparib ([redacted] _____
Pregnancy Test _____

First Response Assessment (at 9 weeks on treatment)
Radiology Evaluation and Tumor Measurements _____

Day 1 of Each Cycle After First Response Assessment
Subject Assessment _____
Weight _____
Vital Signs _____
Concurrent Medications _____
History and Physical _____
Performance Status _____
Adverse Event Evaluation _____
CBC with Differential _____
Serum Chemistries _____
Research Serum Sample _____
Dispense Niraparib ([redacted] _____
Study Drug Accountability _____
Pregnancy Test _____

Every 9 Weeks After First Response Assessment
Radiology Evaluation and Tumor Measurements _____

Off Study
Subject Assessment _____
Weight _____
Vital Signs _____
Concurrent Medications _____
History and Physical _____
Performance Status _____
Adverse Events Evaluation _____
CBC with Differential _____
Serum Chemistries _____
Research Serum Sample _____
Radiology Evaluation and Tumor Measurements _____

Follow-up Assessments
Subject Assessment (may be done via phone) _____
Vital Status Data Collection _____
Development of a Secondary Malignancy _____

Table 5b: Study Activities Checklist for Phase Ia, Schedule #2

Screening (within 4 weeks of Cycle 1, Day 1)

Subject Assessment	
Eligibility Criteria	
Informed Consent	
Demographics	
Medical History	
Concurrent Medications	
Vital Signs	
Height	
Weight	
History and Physical	
Performance Status	
CBC with Differential	
Serum Chemistries	
PT/INR, PTT	
Caris Molecular Profile with DNA Repair Gene Mutation	
Radiology Evaluation and Tumor Measurements	
Tumor Amenable to Biopsy	
Pre-Treatment Biopsy (1) Scheduled/Complete	

Within 2 Weeks of Cycle 1, Day 1

Concurrent Medications	
History and Physical	
Vital Signs	
Weight	
Performance Status	
CBC with Differential	
Serum Chemistries	
Pregnancy Test (within 14 days)	

Cycle 1, Day 1

Subject Assessment	
Concurrent Medications	
Pregnancy Test (within 72 hours)	
Weight	
Vital Signs	
History and Physical	
Performance Status	
Adverse Event Evaluation	
CBC with Differential	
Serum Chemistries	
Research Serum Sample	
Dispense Niraparib [redacted])	

Every Week Until First Response Assessment

Subject Assessment	
Weight	
Vital Signs	
Concurrent Medications	
History and Physical	
Performance Status	
Adverse Event Evaluation	
CBC with Differential	
Serum Chemistries	

Cycle 2, Day 1 (In addition to the above)
Research Serum Sample _____
Dispense Niraparib ([redacted] _____
Study Drug Accountability _____
Pregnancy Test _____

Day 2 of Cycles 2 and 3
Carboplatin treatment _____

Cycle 3, Day 1 (In addition to the above)
Research Serum Sample _____
Study Drug Accountability _____
Dispense Niraparib [redacted] _____
Pregnancy Test _____

First Response Assessment (at 9 weeks on treatment)
Radiology Evaluation and Tumor Measurements _____

Day 1 of Each Cycle After First Response Assessment
Subject Assessment _____
Weight _____
Vital Signs _____
Concurrent Medications _____
History and Physical _____
Performance Status _____
Adverse Event Evaluation _____
CBC with Differential _____
Serum Chemistries _____
Research Serum Sample _____
Dispense Niraparib ([redacted] _____
Study Drug Accountability _____
Pregnancy Test _____

Every 9 Weeks After First Response Assessment
Radiology Evaluation and Tumor Measurements _____

Off Study
Subject Assessment _____
Weight _____
Vital Signs _____
Concurrent Medications _____
History and Physical _____
Performance Status _____
Adverse Events Evaluation _____
CBC with Differential _____
Serum Chemistries _____
Research Serum Sample _____
Radiology Evaluation and Tumor Measurements _____

Follow-up Assessments
Subject Assessment (may be done via phone) _____
Vital Status Data Collection _____
Development of a Secondary Malignancy _____

Table 5c: Study Activities Checklist for Phase Ia, Schedule #3

Screening

Subject Assessment	
Eligibility Criteria	
Informed Consent	
Demographics	
Medical History	
Concurrent Medications	
Vital Signs	
Height	
Weight	
History and Physical	
Performance Status	
CBC with Differential	
Serum Chemistries	
PT/INR, PTT	
Caris Molecular Profile with DNA Repair	
Gene Mutation	
Radiology Evaluation and Tumor Measurements	
Tumor Amenable to Biopsy	
Pre-Treatment Biopsy (1) Scheduled/Complete	

Within 2 Weeks of Week 1, Day 1

Concurrent Medications	
History and Physical	
Vital Signs	
Weight	
Performance Status	
CBC with Differential	
Serum Chemistries	
Pregnancy Test (within 14 days)	

Cycle 1, Day 1

Subject Assessment	
Concurrent Medications	
Pregnancy Test (within 72 hours)	
Weight	
Vital Signs	
History and Physical	
Performance Status	
Adverse Event Evaluation	
CBC with Differential	
Serum Chemistries	
Research Serum Sample	
Dispense Niraparib ([redacted])	

Every Week Until First Response Assessment

Subject Assessment	
Weight	
Vital Signs	
Concurrent Medications	
History and Physical	
Performance Status	
Adverse Event Evaluation	
CBC with Differential	

Serum Chemistries _____

Cycle 2, Day 1 (In addition to the above)
Research Serum Sample _____
Dispense Niraparib ([redacted]) _____
Study Drug Accountability _____
Pregnancy Test _____

Day 2 of Cycles 2 and 3
Carboplatin treatment _____

Cycle 3, Day 1 (In addition to the above)
Research Serum Sample _____
Study Drug Accountability _____
Dispense Niraparib ([redacted]) _____
Pregnancy Test _____

First Response Assessment (at 9 weeks on treatment)
Radiology Evaluation and Tumor Measurements _____

Day 1 of Each Cycle After First Response Assessment
Subject Assessment _____
Weight _____
Vital Signs _____
Concurrent Medications _____
History and Physical _____
Performance Status _____
Adverse Event Evaluation _____
CBC with Differential _____
Serum Chemistries _____
Research Serum Sample _____
Dispense Niraparib ([redacted]) _____
Study Drug Accountability _____
Pregnancy Test _____

Every 9 Weeks After First Response Assessment
Radiology Evaluation and Tumor Measurements _____

Off Study
Subject Assessment _____
Weight _____
Vital Signs _____
Concurrent Medications _____
History and Physical _____
Performance Status _____
Adverse Events Evaluation _____
CBC with Differential _____
Serum Chemistries _____
Research Serum Sample _____
Radiology Evaluation and Tumor Measurements _____

Follow-up Assessments
Subject Assessment (may be done via phone) _____
Vital Status Data Collection _____
Development of a Secondary Malignancy _____

Table 5d: Study Activities Checklist for Phase Ib

Screening

Subject Assessment	
Eligibility Criteria	
Informed Consent	
Demographics	
Medical History	
Concurrent Medications	
Vital Signs	
Height	
Weight	
History and Physical	
Performance Status	
CBC with Differential	
Serum Chemistries	
PT/INR, PTT	
Caris Molecular Profile with DNA Repair Gene Mutation	
Radiology Evaluation and Tumor Measurements	
Tumor Amenable to Biopsy	
Pre-Treatment Biopsy (1) Scheduled/Complete	

Within 2 Weeks of Week 1, Day 1

Concurrent Medications	
History and Physical	
Vital Signs	
Weight	
Performance Status	
CBC with Differential	
Serum Chemistries	
Pregnancy Test (within 14 days)	

Cycle 1, Day 1

Subject Assessment	
Concurrent Medications	
Pregnancy Test (within 72 hours)	
Weight	
Vital Signs	
History and Physical	
Performance Status	
Adverse Event Evaluation	
CBC with Differential	
Serum Chemistries	
PT/INR, PTT	
Research Serum Sample	
Dispense Niraparib	
Study Drug Accountability	

Every Week of First Cycle

Subject Assessment	
Weight	
Vital Signs	
Concurrent Medications	
History and Physical	
Performance Status	

Adverse Event Evaluation _____
CBC with Differential _____
Serum Chemistries _____

Cycle 1, Day 14 (Range Days 10-14)*Subject to change*****
On-Treatment Biopsy (2) Scheduled/Complete _____

Cycle 2 Day 1
PT/INR, PTT _____

Day 1 of Every Cycle Starting Cycle 2
Subject Assessment _____
Concurrent Medications _____
Weight _____
Vital Signs _____
History and Physical _____
Performance Status _____
Adverse Event Evaluation _____
CBC with Differential _____
Serum Chemistries _____
Research Serum Sample _____
Dispense Niraparib _____
Study Drug Accountability _____
Pregnancy Test _____

Day 2 of Every Cycle Starting Cycle 2
Carboplatin treatment _____

Cycle 2, Day 14 (Range Days 10-14)*Subject to change*****
On-Treatment Biopsy (2) Scheduled/Complete _____

Every 9 Weeks
Radiology Evaluation and Tumor Measurements _____

Off Study
Subject Assessment _____
Weight _____
Vital Signs _____
Concurrent Medications _____
History and Physical _____
Performance Status _____
Adverse Events Evaluation _____
CBC with Differential _____
Serum Chemistries _____
PT/INR, PTT _____
Research Serum Sample _____
Radiology Evaluation and Tumor Measurements _____
Off-Treatment Biopsy (4) Scheduled/Complete _____

Follow-up Assessments
Subject Assessment (may be done via phone) _____
Vital Status Data Collection _____
Development of a Secondary Malignancy _____

5.0 DOSAGES AND DISPENSATION OF DRUGS

5.1 Dispensation of Study Drug and Treatments Administered

The study drugs are defined as niraparib and carboplatin. Niraparib will be supplied by GSK. Carboplatin will be supplied by the institution. Patients will receive niraparib by mouth and carboplatin intravenously. Patients will receive sufficient quantities of niraparib for 1 cycle of administration on Day 1 of each cycle. Patients will receive bottles of niraparib from the on-site study coordinator and will be provided with drug diaries (see Appendix E) to record the date and time they took the drugs. Niraparib should specifically be taken with a large glass of water (~250 mL) at the same time each day (including on the days that carboplatin is administered) and should be swallowed whole without crushing, chewing, or opening the pills. If vomiting occurs, no re-dosing of the patient is allowed prior to the next scheduled dose. If doses are not taken within 6 hours of the intended time, the dose should be skipped and not replaced or made up on a subsequent day. Patients should be instructed to store niraparib at room temperature. Subjects should return bottles of niraparib (empty, partially filled, or full) and their diaries (See Appendix E) to the study site prior to start of next cycle and at the final visit. Carboplatin will be administered IV on day 2 of each cycle (or other variation as outlined above in Section 4.1.1) at each patient's respective on-site infusion center. Patients should receive a minimum of ondansetron 8mg IV and dexamethasone 8mg IV prior to carboplatin, and the infusion should be given over 60 minutes. The carboplatin infusion should be prepared by each treating institution the day of infusion and refrigerated prior to drug delivery. Concurrent intravenous fluids with 0.9% normal saline is recommended for a total of 1000 mL, though not required. Orders for carboplatin will be written on the day of treatment at each participating institution for a target AUC of 2-4, as defined in Dose Escalation Table 1(or per the alternative schedule if employed).

5.2 Packaging and Labeling of Niraparib

Niraparib will be packaged in bottles containing 100 mg tablets or capsules with a sufficient quantity in the bottle for one cycle, plus enough for one extra day (see Table 6).

Table 6. Dispensation of Niraparib by Dose Level

Dose Level	Dose	100 mg Tablets Dispensed
1	[redacted]	[redacted]
2		
3		
4		
5		
6		
7		
8		
9		

Each bottle will be labeled with an open-label white single panel or booklet label that will include, but is not limited to, the following information:

1. Protocol number
2. Drug identification
3. Number of capsules
4. Storage conditions
5. Dosing instructions
6. Blank spaces to write the subject's identification number, initials and date dispensed

Each bottle label must remain affixed to the bottle.

5.3 Storage and Disposition of Niraparib and Carboplatin

Niraparib should be stored at room temperature and should be protected from light and moisture. Carboplatin should be refrigerated at the participating treatment center following preparation on day of treatment (prior to preparation vials can be stored at room temperature, protected from light). Niraparib will be packaged in high-density polyethylene bottles with child-resistant plastic closures. All clinical supplies must be stored in a secure place until they are dispensed for subject use or are returned to the participating center's pharmacy. Investigational products are for investigational use only, and are to be used only within the context of this study.

The clinical supplies supplied for this study must be maintained under adequate security and stored under conditions specified on the label. Destruction of used and unused study drug will be performed at the site.

5.4 Treatment Compliance

Subjects will be instructed to return all bottles of niraparib to the study site personnel prior to each cycle and at the final visit. The study site personnel will document the bottles of study drug returned and the number of capsules per bottle, according to institutional policy. If the number of capsules taken and the number of capsules returned do not add up to the number of capsules dispensed, an explanation will be provided. Unless otherwise directed by the principal investigator, a subject will be considered compliant with study drug if 85% of the assigned dose is taken during a cycle. Doses of carboplatin will be recorded per treatment institution and tracked by the on-site study coordinator. Patients may not miss a dose of carboplatin, but are allowed to receive dose modifications as outlined in Section 4.1.1.

5.5 Drug Accountability

The investigator or designee will verify that niraparib supplies are received intact and in the correct amounts. A signed and dated Proof of Receipt (POR) or similar document will support documentation of the receipt of supplies. An accurate running inventory of niraparib will be maintained by the site, and will include the lot number, POR number(s), the bottle numbers, and the date study drug was dispensed for each subject. Upon completion or termination of the study, all original containers (empty or containing unused study drug) will be returned to the manufacturer or destruction of used and unused study drug will be performed at the site. Labels must remain attached to the containers. The investigator or his/her designated representative agrees not to supply study medication to any persons not enrolled in the study or not named as a sub-investigator. The site will record the lot number(s) and doses of niraparib and carboplatin given to each subject.

5.6 Selection of Doses in the Study (Niraparib Investigator's Brochure[90])

Initial doses of niraparib in this study are based on data from other PARP inhibitors in combination with chemotherapy including carboplatin, and on Phase I data of niraparib alone and in combination with other chemotherapy regimens (temozolomide and carboplatin). [redacted] We therefore have selected an initial dose of niraparib of [redacted], a dose that allows for appropriate PARP inhibition, with carboplatin AUC of 2, a lower dose than previously studied in a niraparib combination regimen. We believe this starting dose will provide appropriate efficacy with a low likelihood for significant DLTs.

5.7 Carboplatin Dosing

Carboplatin dosing to a goal AUC of 2 – 4 (as per the Dose escalation Tables) will be based off of creatinine clearance per the Cockroft-Gault formula. Dose capping of carboplatin may be carried out according to local institutional protocols.

6.0 SAFETY VARIABLES AND TOXICITY ASSESSMENT

The Principal Investigator or Sub-investigators will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 5.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

6.1 Adverse Events Assessment

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All adverse events will be followed to a satisfactory conclusion.

6.2 Study Monitoring

6.2.1 Data Safety Monitoring Committee at Georgetown

The Georgetown Lombardi Comprehensive Cancer Center (LCCC) will be responsible for the data and safety monitoring of this trial. As this study is an investigator initiated Phase I study utilizing FDA-approved on label, and off label therapies, it is considered a high risk study which requires real-time monitoring by the PI and study team and quarterly reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator, Dr. Isaacs, and the Study Chairs will review the data including safety monitoring at their monthly teleconferences with participating sites.

SAEs are required to be reported to the local and/or to the Georgetown IRB, per IRB reporting guidelines. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 3 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC Associate Director for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the Associate Director for Clinical Research.

Of note, the DSMC will also review the safety data of the patients enrolled outside of Georgetown University. Georgetown University's LCCC Consortium IIT Office will be tasked with the job of collecting all primary source documentation for patients enrolled outside of Georgetown University. In addition, the data managers at each site will be entering data into the Georgetown database, so that all data will be available for the DSMC at Georgetown to review. Records should be sent via email to the Georgetown University's LCCC Consortium IIT Office, and Dr. Isaacs.

6.3 Adverse Event and Toxicity Definitions

6.3.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product. Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*e.g.*, surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

AEs may also include signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

A ***treatment-emergent*** adverse event will be defined as any new AE that begins, or any preexisting condition that worsens in severity during the Treatment Period after at least 1 dose of study medication and throughout the treatment period until 30 days after cessation of study treatment for non-serious AEs or until 90 days after cessation of study treatment for SAEs and AESIs (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy).

6.3.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to the DSMC as a SAE within 24 hours of the site being made aware of the serious adverse event.

1) **Death of Subject** An event that results in the death of a subject.
2) **Life-Threatening** An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
3) **Hospitalization** (unless planned for observation, protocol compliance, elective procedures, social reasons) **or**
4) **Prolongation of Hospitalization** An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
5) **Congenital Anomaly** An anomaly detected at or after birth, or any anomaly that results in fetal loss.

6) **Persistent or Significant Disability/Incapacity** An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
7) **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
8) **Spontaneous Abortion** Miscarriage experienced by study subject.

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

6.3.3 Adverse Events of Special Interest

Selected non-serious 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 Sponsor Institution and to GSK regardless of causality assessment to study drug.

AESIs for this trial are defined as:

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

AESI should be collected and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the Sponsor throughout the Follow-up Assessment Period

6.3.5 Adverse Event Severity

The study investigator will rate the severity of each adverse event according to the NCI CTCAE Version 5.0. For adverse events not captured by the NCI CTCAE Version 5.0, the following should be used:

1) **Grade 1 (Mild)** The adverse event is transient and easily tolerated by the subject.
2) **Grade 2 (Moderate)** The adverse event causes the subject discomfort and interrupts the subject's usual activities.
3) **Grade 3/4 (Severe or Life Threatening)** The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.
4) **Grade 5 (Severe, Resulting in Death)** The adverse event resulted in death of the subject.

6.3.6 Relationship to Study Drug

6.3.6.1 Assessment of Toxicity Relatedness to Study Medications

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug(s).

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

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

6.3.6.2 Attribution of Relationship to Study Medications

For every adverse event, the investigator must also attribute whether the adverse event was due to (A) carboplatin, (B) niraparib, (C) both study medications, or (D) other causes.

If an investigator's opinion of probably not or not related to study drug(s) is given, an Other cause of event must be provided by the investigator for the adverse event.

6.3.6.3 Assessment of Expectedness

For every adverse event, the investigator must also attribute whether the adverse event is 'expected' or 'unexpected'.

- An AE will be considered *unexpected* if the nature, severity, or frequency of the event is not consistent with the risk information provided in the Reference Safety Information of the effective Investigator Brochure (IB).
- For Niraparib:
    - While events of MDS/AML are considered expected, fatal MDS/AML is considered unexpected for the purposes of reporting to regulatory authorities, investigators and ethics committees/review boards, as applicable.
    - Similarly, while events of neutropenic sepsis and hypertension are considered expected, **life-threatening** neutropenic sepsis and **life-threatening** hypertension are considered unexpected for the purposes of reporting to regulatory authorities, investigators and ethics committees/review boards, as applicable.
    - All fatal Adverse Drug Reactions (ADRs) are considered unexpected.
    - The following life threatening ADRs are considered expected: thrombocytopenia, anemia, neutropenia, pancytopenia, leukopenia, and myelodysplastic syndrome/ acute myeloid leukemia

6.3.7 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) additional reporting requirements are described below. These types of reports are referred to as (SUSARs).

a. If the SUSAR is fatal or life-threatening, associated with the use of the study treatment, and unexpected, Regulatory Authorities and IECs will be notified 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).
b. If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the study treatment, and unexpected, Regulatory Authorities and IECs will be notified within 15 calendar days after the Investigator learns of the event.

The Institution 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.

6.4 Adverse Event Collection Period

All adverse events reported from the time of the administration of study drug until 30 days following discontinuation of therapy has elapsed will be collected, whether elicited or spontaneously reported by the subject. All serious adverse events and adverse events of special interest will be collected from the time the subject signed the study-specific informed consent until at least 90 days after cessation of study treatment for (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy).

6.5 Adverse Event Reporting

In the event of a serious adverse event, whether related to study drugs, study procedures such as a biopsy, or even if not directly related to any study intervention, the investigator will notify the IRB if required by local institutional IRB reporting guidelines. Furthermore, the investigator will forward all treatment emergent SAE reports regardless of causality, to GSK within 24 hours of becoming aware of the event, by email to [redacted] or by facsimile to GSK at [redacted]. The institution will forward initial and any follow-up reports.

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to GSK within 24 hours. SAEs brought to the attention of the investigator at any time after cessation of the study drugs and considered by the investigator to be related or possibly related to the study drugs must be reported to the IRB if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (*e.g.*, procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

For patients enrolled outside of Georgetown University, serious adverse events will also be reported, and all supporting documentation sent (faxed or emailed) to Georgetown University's LCCC Consortium IIT Office and to the study PI, Dr. Isaacs within 24 hours. Records should be sent by secure email to the LCCC Consortium IIT Office and to Dr. Isaacs [redacted]) to confirm receipt of those records.

6.6 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 Institution or qualified designee to GSK within 1 working day of first becoming aware of the possible defect to GSK QA at [redacted]. 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.

6.7 Pregnancy

Pregnancies (and pregnancy outcomes) occurring in a female patient or a female partner of a male patient must be reported to the Institution within 24 hours. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Spontaneous abortions should always be reported as SAEs. The Investigator should follow-up with the study patient or the female partner of the study patient until delivery or termination of pregnancy, even if the patient was withdrawn from the clinical study or the clinical study was completed. GSK will be informed of all pregnancy outcomes.

In the event of a positive pregnancy test result, study drugs will be immediately discontinued. The investigator must report the positive pregnancy test within 24 hours of the site becoming aware of the pregnancy to the IRB and to [redacted]

Reporting pregnancy to GSK should occur on an Initial Pregnancy Report Form. The Investigator must follow-up all pregnancies, document the course and the outcome, and report this information to the Sponsor Institution and to GSK on a Pregnancy Outcome Report Form within 24 hours of becoming aware of the outcome- even if the patient was withdrawn from the study or the study has finished.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form, reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor Institution and GSK within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

For patients enrolled outside of Georgetown University, documentation should be emailed to Georgetown University's LCCC Consortium IIT Office and to the study PI, Dr. Isaacs, within 24 hours.

Patients should also notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within 180 days after the treatment period. Male participants should notify the investigator if their partner becomes pregnant during the treatment phase or within 90 days after treatment. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected, and the status of the mother and child should be reported to the IRB and GSK after delivery.

6.8 Potential Risks of Niraparib

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

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

The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients receiving niraparib: tachycardia, dry mouth, mucosal inflammation, aspartate aminotransferase increased, alanine aminotransferase increased, and photosensitivity reaction.

Posterior reversible encephalopathy syndrome (PRES) has been observed in 0.1% of patients treated with Niraparib. If PRES is suspected, promptly discontinue Niraparib.

Hypertension, Including Hypertensive Crisis

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Pre-existing hypertension should be adequately controlled before starting niraparib treatment. Blood pressure and heart rate should be monitored at least weekly for the first two 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 development program, most cases of hypertension were 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 (MRI). 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.

6.8.1 Description of selected adverse reactions

Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia) including clinical diagnoses and/or laboratory findings generally occurred early during niraparib treatment with the incidence decreasing over time. The median time to onset of thrombocytopenia regardless of grade was 22 days. Most events were transient with thrombocytopenia resolving within 10 days. In the clinical program, thrombocytopenia was managed with laboratory monitoring and dose modification (see Section 6.9). Discontinuation due to thrombocytopenia occurred in 3% of patients. The median time to onset of anemia of any grade was 42 days, and for Grade 3/4

events was 85 days. The median duration of anemia of any grade was 63 days and was considerably shorter for Grade 3/4 anemia at 8 days. Discontinuation due to anemia occurred in 1% of patients. Most patients did not receive treatment for neutropenia events. Discontinuation due to neutropenia events occurred in 2% of patients.

Hypertension, including hypertensive crisis, has been reported with niraparib therapy. In the clinical program, hypertension was readily managed with anti-hypertensive medication. Discontinuation due to hypertension occurred in <1% of patients.

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with fatal outcome, have been reported in a small number of patients who received niraparib or placebo. In the Phase 3 international trial ENGOTOV16 / NOVA, the incidence of MDS/AML in patients who received niraparib (1.4%) was similar to that in patients who received placebo (1.1%). The duration of niraparib treatment in patients prior to developing MDS/AML varied from 1 month to >2 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received multiple platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with niraparib, niraparib should be discontinued and the patient treated appropriately.

6.9 Toxicity Management and Dose Adjustments

6.9.1 Dose Limiting Toxicity (DLT) Definitions

Toxicities will be defined ***in the Phase Ia portion of the study*** as DLTs if they are included below (as defined by NCI CTCAE v.5.0) and they occur ***during the first two cycles of therapy*** and are deemed ***related to the study regimen*** as assessed by the investigator. In addition, any toxicity which results in withholding of therapy for ≥ 4 weeks will be treated as a DLT.

Table 8. Criteria for Defining DLTs in the Phase Ia Portion of Study Related to Niraparib or Carboplatin

Toxicity	**DLT** (per CTCAE v. 5.0)
Hematology	≥ Grade 4 neutropenia (ANC < 500/μL) lasting ≥ 7 consecutive days
	Grade 3 or 4 febrile neutropenia
	≥ Grade 4 thrombocytopenia
	Grade 3 thrombocytopenia with clinically significant bleeding
	Grade 4 anemia or Grade 3 anemia requiring blood transfusion
Cardiac	≥ Grade 3 cardiac toxicity, clinical signs of cardiac disease such as unstable angina, myocardial infarction, or troponin ≥ Grade 3
Gastrointestinal	≥ Grade 3 vomiting ≥ 48 hours *despite optimal anti-emetic therapy*
	≥ Grade 3 diarrhea ≥ 48 hours *despite optimal anti-diarrheal therapy*
	(Optimal therapy for vomiting and diarrhea should be based on institutional guidelines with consideration of the prohibited medications listed in these protocol guidelines).
Hepatobiliary	≥ Grade 2 total bilirubin > 7 consecutive days
	≥ Grade 3 total bilirubin
	≥ Grade 2 AST/ALT **AND** ≥ Grade 2 bilirubin elevation of any duration in the absence of liver metastases
	≥ Grade 3 AST/ALT for > 4 consecutive days
	Grade 4 ALT or AST
Renal	≥ Grade 3 serum creatinine
Non-hematologic, non-hepatic adverse events	≥ Grade 3 except for the following exceptions:
Exceptions to DLT criteria	Grade 3 alopecia
	< 7 days of Grade 3 fatigue
	Grade 3 fever or infection without neutropenia < 5 days duration
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
Other	Any toxicity which results in withholding of therapy for > 4 weeks

If a DLT is experienced, patients should be monitored as follows:

- **Hematologic:** daily blood counts with CBC until toxicity is Grade 3 or less, then weekly blood counts for CBC until Grade 1 or less with the following exceptions:
    - If febrile Grade 3 or 4 neutropenia, patient should be hospitalized for antibiotics and clinical monitoring (including daily blood counts for CBC)
    - If Grade 3 thrombocytopenia with bleeding, daily blood counts with CBC until bleeding ceases, then weekly blood counts for CBC until Grade 1 or less
- **Cardiac Disease:** prompt cardiac consultation and management per recommendations
- **Gastrointestinal:** daily symptom evaluation (clinic or telephone) until toxicity is ≤ Grade 2, and then weekly evaluation until Grade 1 or less (clinic or telephone)
- **Hepatobiliary:** daily serum liver function tests until toxicity is:
    - *Grade 3 or less* for isolated Grade 4 AST/ALT elevation or isolated Grade 4 alkaline phosphatase elevation, then weekly serum liver function tests until Grade 1 or less
    - *Grade 2 or less* for isolated Grade 3 or 4 total bilirubin elevation, then weekly serum liver function tests until Grade 1 or less

  For combined ≥ Grade 2 AST/ALT elevation **AND** ≥ Grade 2 bilirubin elevation in the absence of liver metastases, daily serum liver function tests until toxicity is Grade 2 or less, then weekly serum liver function tests until Grade 1 or less. If initial toxicity is Grade 2, proceed with weekly serum liver function tests until Grade 1 or less only
- **Renal:** daily serum creatinine measurement until toxicity is ≤ Grade 2, and then weekly serum creatinine measurement until Grade 1 or less
- **Other:** daily evaluation by labwork or symptom evaluation (clinic or telephone) based on toxicity until ≤ Grade 2, and then weekly evaluation by labwork or symptom evaluation (clinic or telephone) based on toxicity until Grade 1 or less

6.9.2 Therapeutic Dosing in Response to DLTs

6.9.2.1 Schedule #1

According to Schedule #1, niraparib will be given on [redacted] of each cycle, and carboplatin is given on D2 beginning with Cycle 2. If a DLT is experienced, guidelines should be followed as listed in Table 8 and 9. When toxicity resolves to Grade 1 or less (within 28 days), the patient may resume treatment at the dose level below the previous dose level.

- If the DLT is experienced during Cycle 1 and resolves to Grade 1 or less (within 28 days), the patient may resume at the dose level below beginning at Cycle 1
- If the DLT is experienced during Cycle 2 PRIOR to carboplatin dose and resolves to Grade 1 or less (within 28 days), the patient may resume the dose level below beginning at Cycle 1
- If the DLT is experienced during Cycle 2 AFTER carboplatin dose and resolves to Grade 1 or less (within 28 days), the patient may resume the dose level below beginning at Cycle 2, and so on

For the Phase Ib portion, if toxicity hinders biopsy accession, a biopsy should be attempted at the appropriate time within the next dose level treatment schedule.

6.9.2.2 Schedule #2

According to Schedule #2, niraparib will be given on [redacted] of each cycle, and carboplatin is given on D2 beginning with Cycle 2. If a DLT is experienced, guidelines should be followed as listed in Table 8 and 9. When toxicity resolves to Grade 1 or less (within 28 days), patient may resume treatment at the dose level below the previous dose level.

- If the DLT is experienced during Cycle 1 and resolves to Grade 1 or less (within 28 days), the patient may resume the dose level below beginning at Cycle 1
- If the DLT is experienced during Cycle 2 PRIOR to carboplatin dose and resolves to Grade 1 or less (within 28 days), the patient may resume the dose level below beginning at Cycle 1
- If the DLT is experienced during Cycle 2 AFTER carboplatin dose and resolves to Grade 1 or less (within 28 days), patient may resume the dose level below beginning at Cycle 2, and so on

For the Phase Ib portion, if toxicity hinders biopsy accession, a biopsy should be attempted at the appropriate time within the next dose level treatment schedule.

6.9.2.3 Schedule #3

According to Schedule #3, niraparib will be given on [redacted] of each cycle, and carboplatin is given on D2 and D9 beginning with Cycle 2. If a DLT is experienced, guidelines should be followed as listed in Table 8 and 9. When toxicity resolves to Grade 1 or less (within 28 days), patient may resume treatment at the dose level below the previous dose level.

- If the DLT experienced during Cycle 1 and resolves to Grade 1 or less (within 28 days), the patient may resume the dose level below beginning at Cycle 1
- If the DLT is experienced during Cycle 2 PRIOR to D2 carboplatin dose and resolves to Grade 1 or less (within 28 days), the patient may resume the dose level below beginning at Cycle 1
- If the DLT is experienced during Cycle 2 AFTER D2 or D9 carboplatin dose and resolves to Grade 1 or less (within 28 days), the patient may resume the dose level below beginning at Cycle 2, and so on

For the Phase Ib portion, if toxicity hinders biopsy accession, a biopsy should be attempted at the appropriate time within the next dose level treatment schedule.

6.10 General Management of Significant Toxicities

6.10.1 Significant Toxicities Management

The following are general guidelines for dose reduction, delay and discontinuation of the study drugs if a subject experiences a DLT, as per Table 8, or an adverse event that is specifically outlined in Table 9 and is deemed possibly, probably, or definitely related to study therapy:

- All treatment should be discontinued/delayed until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 at the time of study entry
- Subjects may delay retreatment for up to 4 weeks to allow the toxicity to resolve. If the toxicity requiring dose interruption has not resolved completely or to CTCAE Grade 1 (or to baseline if Grade 2 at time of study entry) during the maximum 4-week dose interruption period, the patient must permanently discontinue treatment on study
- Patients may restart therapy if toxicity(ies) resolve to Grade 1 or lower (or to baseline if Grade 2 at time of study entry), but at a lower dose level as per Table 1 for both Phase Ia and Phase Ib.
- No more than two dose level reductions are allowed.
- If patients are at the lowest dose level and a dose reduction is required, then that patient will be taken off study.
- If a dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC also will be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume.
- Any patient requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a dose reduction upon recovery if study treatment is resumed.
- The patient must be referred to a hematologist for further evaluation (1) if frequent transfusions are required or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less after 4 weeks.
- For major surgery while on treatment, up to 28 days of study treatment interruption is allowed.
- Once the dose of study treatment has been reduced, any re-escalation must be discussed with the medical monitor.
- All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded.

Table 9. Dose Modifications for Toxicities Related to Niraparib or Carboplatin

The following table defines the therapeutic management of patients in the trial.

Please note that these rules cover BOTH toxicities that meet the definition of a DLT, and NON-DLT-defining toxicities for both the Phase Ia and Phase Ib portions of the trial. The following are general guidelines for dose reduction, delay and discontinuation of the study drugs if a subject experiences an adverse event that is specifically outlined in Table 9 and is deemed possibly, probably, or definitely related to study therapy:

Hematologic
Thrombocytopenia[1]

Platelet count $\geq$ 100 x 10^9/L	No dose adjustment required
Grade 1 (75 x 10^9/L – 99 x 10^9/L)	Hold niraparib and carboplatin until platelet counts are $\geq$ 100 x 10^9/L with weekly blood counts for CBC monitored until recovery. Study drugs may then be resumed at the same dose if resolved in $\leq$ 7 days. If requires > 7 days to resolve, resume at a reduced dose (the previous dose level as outlined in Phase Ia).
Grade 2 & 3 ($\leq$ 74 x 10^9/L)	Hold niraparib and carboplatin until platelet counts are $\geq$ 100 x 10^9/L with weekly blood counts for CBC monitored until recovery. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia). Discontinue study drugs if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient was already receiving the lowest dose.
Second occurrence of platelet count $\leq$100 x 10^9/L (any grade)	Hold niraparib and carboplatin until platelet counts are $\geq$ 100 x 10^9/L with weekly blood counts for CBC monitored until recovery. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia). Discontinue study drugs if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient was already receiving the lowest dose.
Grade 4 ($\leq$ 25 x 10^9/L)	Hold niraparib and carboplatin until platelet counts are $\geq$ 100 x 10^9/L with daily blood counts for CBC monitored until platelet count > 25 x 10^9/L, and then weekly blood counts for CBC until recovery. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia) if resolved within 28 days. Discontinue study drugs if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient was already receiving the lowest dose.
Neutropenia (ANC)	
Grade 1 (≥ 1.5 x 10^9/L)	No dose adjustment required
Grade 2 (≥ 1.0 – < 1.5 x 10^9/L)	Hold niraparib and carboplatin until recovery ≥ 1.5 x 10^9/L with weekly blood counts for CBC. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia). Discontinue study drugs if the neutrophil count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient was already receiving the lowest dose.
Grade 3 (≥ 0.5 – < 1.0 x 10^9/L)	Hold niraparib and carboplatin until recovery ≥ 1.5 x 10^9/L with weekly blood counts for CBC. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia). Discontinue study drugs if the neutrophil count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient was already receiving the lowest dose.
Grade 4 ($\leq$ 5 x 10^9/L)	Hold niraparib and carboplatin until recovery ≥ 1.5 x 10^9/L with daily blood counts for CBC monitored until ANC ≥ 0.5 – < 1.0 x 10^9/L, and then weekly blood counts for CBC until recovery. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia). Discontinue study drugs if the neutrophil count has not returned to acceptable

	levels within 28 days of the dose interruption period, or if the patient was already receiving the lowest dose. If recurs at Grade 4: Discontinue all therapy (off study)
Febrile neutropenia	
Grade 3 (ANC < 1.0 x 10^9/L with a single temperature > 38.3 °C (101 °F) or a sustained temperature of ≥ 38.3 °C (101 °F) for more than 1 hour	Hold niraparib and carboplatin until recovery ≥ 1.5 x 10^9/L with weekly blood counts for CBC and afebrile. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia). If recurs: Discontinue all therapy (off study)
Grade 4 (life-threatening consequences, urgent intervention indicated)	Discontinue all therapy (off study)
Anemia (hemoglobin)	
Grade 1 (≥ 10.0 – LLN g/dL)	No dose adjustment required
Grade 2 (≥ 8.0 – < 10.0 g/dL)	No dose adjustment required
Grade 3 (< 8.0 g/dL)	Hold niraparib and carboplatin until recovery to ≥ 9.0 g/dL with weekly blood counts for CBC. Packed red blood cell transfusions allowed to achieve a hemoglobin of ≥ 9.0g/dL. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia). Discontinue study drugs if the hemoglobin count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient was already receiving the lowest dose.
Grade 4 (life-threatening consequences, urgent intervention indicated)	Hold niraparib and carboplatin until recovery ≥ 9.0g/dL with daily blood counts for CBC until Grade 3 anemia, and then weekly blood counts for CBC monitored until recovery. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia). Discontinue study drugs if the hemoglobin count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient was already receiving the lowest dose. If recurs: Discontinue all therapy (off study)
Confirmed diagnosis of MDS or AML	Discontinue all therapy (off study)

Hepatotoxicity	
Total bilirubin elevation without AST/ALT increase above baseline value[2]	
Grade 1 (> ULN – 1.5 x ULN) confirmed on repeat 48-72 hours later *ONLY IF GRADE 0 AT BASELINE*	Maintain dose level with liver enzymes and bilirubin tests monitored weekly until normalizes
Grade 2 (> 1.5 – 3.0 x ULN)	Hold niraparib and carboplatin until ≤ 1.5 x ULN monitored with weekly blood tests for liver enzymes and bilirubin tests. Study drugs may then be resumed at the same dose if resolved to ≤ Grade 1 in ≤ 14 days. If it requires > 14 days or toxicity recurs, re-initiate niraparib and carboplatin at a reduced dose (the previous dose level as outlined in Phase Ia). Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks following re-initiation If recurs at reduced dose level, discontinue all therapy (off study)
Grade 3 (> 3.0 – 10.0 x ULN)	Hold niraparib and carboplatin until ≤ 1.5 x ULN monitored with weekly blood tests for liver enzymes and bilirubin tests. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia) if resolved to ≤ Grade 1 in ≤ 21 days. If resolved to ≤ Grade 1 in > 21 days or toxicity recurs, discontinue all therapy (off study) Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks following re-initiation
Grade 4 (> 10.0 x ULN)	Discontinue all therapy (off study)
AST or ALT elevation without bilirubin elevation > 2 x ULN	

Same grade as baseline or increase from baseline Grade 0 to Grade 1 confirmed 48-72 hours later	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1
Increase from baseline Grade 0 or 1 to Grade 2 (> 3.0 – 5.0 x ULN)	Hold niraparib and carboplatin until LFTs resolve to ≤ baseline value with weekly blood tests for liver enzymes. Study drugs may then be resumed at the same dose if resolved to baseline value in ≤ 14 days. If resolved to ≤ baseline value in > 14 days or toxicity recurs, re-initiate niraparib and carboplatin at a reduced dose (the previous dose level as outlined in Phase Ia). Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks following re-initiation If recurs at reduced dose level or recovery to ≤ baseline value in > 14 days, discontinue all therapy (off study)
Increase from baseline Grade 0 or 1 to Grade 3 (> 5.0 – 20.0 x ULN)	Hold niraparib and carboplatin until LFTs resolve to ≤ baseline value with weekly blood tests for liver enzymes. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia) if resolved to baseline value in ≤ 21 days. Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks following re-initiation If recurs at reduced dose level or recovery to ≤ baseline value in > 21 days, discontinue all therapy (off study)
Increase from baseline Grade 2 (i.e., in a patient with liver metastases) to Grade 3 (> 5.0 – 20.0 x ULN)	Hold niraparib and carboplatin until LFTs resolve to ≤ baseline value with weekly blood tests for liver enzymes. Study drugs may then be resumed at a reduced dose (the previous dose level as outlined in Phase Ia) if resolved to baseline value in ≤ 21 days. Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks following re-initiation If recurs at reduced dose level or recovery to ≤ baseline value in > 21 days, discontinue all therapy (off study)
Grade 4 (> 20.0 x ULN)	Discontinue all therapy (off study)
AST or ALT and concurrent bilirubin elevation	
Normal ALT or AST or total bilirubin at baseline: AST or ALT ≥ Grade 2 with total bilirubin > 2 x ULN without evidence of cholestasis OR Elevated AST or ALT or total bilirubin at baseline: baseline: [AST or ALT >2 x baseline AND > 3.0 x ULN] OR [AST or ALT 8.0 x ULN]- whichever is lower-combined with [total bilirubin 2x baseline AND > 2.0 x ULN]	Discontinue all therapy (off study)
<u>All Other Adverse Reactions</u>	

Grade 1	No dose adjustment recommended, initiate appropriate medical therapy and monitor
Grade 2 (unless Grade 2 at baseline)	Hold niraparib and carboplatin until ≤ Grade 1, treat with appropriate medical therapy and monitor, re-initiate at same dose If recurs at Grade 2, hold niraparib and carboplatin until ≤ Grade 1, re-initiate niraparib and carboplatin at a reduced dose (previous dose level as outlined in Phase Ia).
Grade 3	Hold niraparib and carboplatin until ≤ Grade 1, treat with appropriate medical therapy and monitor, re-initiate niraparib and carboplatin at a reduced dose (previous dose level as outlined in Phase Ia). If recurs at Grade 3, discontinue all therapy (off study)
Grade 4	Discontinue all therapy (off study), treat with appropriate medical therapy

[1] For patients with platelet count ≤ 10,000/μL, prophylactic platelet transfusion per guidelines may be considered.{Schiffer, 2001 #154}{Slichter, 2007 #155}. For patients taking anticoagulation or antiplatelet drugs, consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as ≤ 20,000/μL.

[2] Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.

6.10.2 Management of Phase Ib Toxicities in Alternative Schedules

6.10.2.1 Schedule #1

According to Schedule #1, niraparib will be given on [redacted] of each cycle, and carboplatin is given on D2 beginning with Cycle 2. If a toxicity is experienced that requires treatment hold, guidelines should be followed as listed in Table 9. Treatment should resume at the same Cycle from whence the toxicity was noted, but perhaps at a reduced dose (per Table 9). If toxicity hinders biopsy accession, a biopsy should be attempted at the appropriate time when treatment is resumed.

6.10.2.2 Schedule #2

According to Schedule #2, niraparib will be given on [redacted] of each cycle, and carboplatin is given on D2 beginning with Cycle 2. If a toxicity is experienced that requires treatment hold, guidelines should be followed as listed in Table 9. Treatment should resume at the same Cycle from whence the toxicity was noted, but perhaps at a reduced dose (per Table 9). If toxicity hinders biopsy accession, a biopsy should be attempted at the appropriate time when treatment is resumed.

6.10.2.3 Schedule #3

According to Schedule #3, niraparib will be given on [redacted] of each cycle, and carboplatin is given on D2 and D9 beginning with Cycle 2. If a toxicity is experienced that requires treatment hold, guidelines should be followed as listed in Table 9. Treatment should resume at the same Cycle from whence the toxicity was noted, but perhaps at a reduced dose (per Table 9). If toxicity is noted on D8 limiting the second treatment with niraparib and/or carboplatin, then the Cycle should be resumed at D1 once the toxicity resolves, perhaps at a reduced dose (per Table 9). If toxicity hinders biopsy accession, a biopsy should be attempted at the appropriate time when treatment is resumed.

7.0 MEASUREMENT OF EFFECT

7.1 Definitions

Tumor response and/or disease progression will be assessed by a CT scan (or other appropriate modalities such as MRI consistent with the modality used prior to treatment) utilizing RECIST v1.1 criteria. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria. Assessments will be performed within 4 weeks before screening every 9 weeks thereafter, and at the final visit, if not performed within the last four weeks.

7.1.1 Safety and Tolerability Evaluable

For the Phase Ia portion, for a patient to be evaluable for safety, tolerability, and assessment of dose-limiting toxicities, the patient must complete the first two cycles. Any patient who is taken off study for any reason other than toxicity (or death related to toxicity) ***will not be*** considered evaluable for assessment of safety, tolerability, and assessment of dose-limiting toxicity, and must be replaced.

7.1.2 Response Evaluable

A patient who initiates therapy per protocol, and is taken off study for disease progression or clinical progression, including death related to the underlying solid tumor malignancy (as determined by the treating oncologist) ***will be*** considered evaluable for response assessment. However, patients who have initiated therapy and who withdraw from the study for any reason other than clinical or radiographic progression, or death believed unrelated to their underlying solid tumor malignancy ***will not be*** considered evaluable for response. Reasons for patients who have initiated therapy, but are no longer evaluable for response could include (but are not limited to):

- The patient cannot tolerate therapy despite dose modifications, and there is no evidence of clinical/radiographic disease progression at the time of stopping therapy
- An unexpected and/or unrelated medical illness, such as a stroke or myocardial infarction that is considered unrelated to the underlying solid tumor malignancy
- An unexpected trauma or death that is considered unrelated to the underlying solid tumor malignancy

7.1.3 Disease Parameters

7.1.3.1 Measurable Disease

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

7.1.3.2 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques (CT, MRI, x-ray) or as >10 mm with spiral CT scan. Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

7.1.3.3 Non-measurable disease

All other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis and cystic lesions are considered non-measurable disease.

All measurements should be taken and recorded in metric notation, using a ruler or calipers. 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. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is required.

7.2 Methods of Measurement

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice

thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. For accurate objective response evaluation, ultrasound should not be used to measure tumor lesions. However, ultrasound is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

7.2.1 Baseline Documentation of "Target" and "Non-Target" Lesions

7.2.1.1 Target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

7.2.1.2 Non-target lesions

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

7.3 Response Criteria

7.3.1 Evaluation of Tumor Response-Measurable Disease

7.3.1.1 Complete Response (CR)

The disappearance of all known disease, determined by two observations not less than 4 weeks apart. There can be no appearance of new lesions.

7.3.2.2 Partial Response (PR)

A 30% or more decrease in the sum of the LD of target lesions that have been measured to determine the effect of therapy by two observations not less than 4 weeks apart. There can be no appearance of new lesions.

7.3.2.3 Progressive Disease (PD)

At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions resulting in at least a 20% increase in the sum of the LD of target lesions, and/or an unequivocal progression of non-target lesions resulting in at least a 20% increase in the sum of the LD of target lesions.

7.3.2.4 Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

7.4 Evaluation of Best Overall Response

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

Table 10: Response Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	>4 wks confirmation
CR	Non-CR/Non-PD	No	PR	>4 wks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once >4 wks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

7.5 Definition of Disease Progression

Disease progression will be defined as:

1) Radiologic progression of disease by RECIST v1.1 criteria.
2) Clinical progression as determined by the investigator, which may be characterized as, but is not limited to:
    a. Increase of at least 2 points in ECOG performance status attributable to cancer progression.
    b. Requirement for palliative chemotherapy or surgery.
3) Death from disease progression

8.0 STATISTICAL CONSIDERATIONS

8.1 Objectives

8.1.1 Primary Objective of the Phase Ia Portion:

To identify the RP2D and schedule of niraparib plus carboplatin for patients with homologous recombination deficient advanced solid tumor malignancies

8.1.2 Primary Objective of the Phase Ib Portion:

To determine the anti-tumor efficacy of niraparib plus carboplatin in a non-disease specific cohort of patients with homologous recombination deficient advanced solid tumor malignancies, as determined by RECIST v1.1

8.1.3 Secondary Objectives:

Clinical:

a. To evaluate the safety and tolerability of niraparib plus carboplatin
b. To determine evidence of any disease specificity with this combination
c. To assess the anti-tumor efficacy of combined therapy as determined by RECIST v1.1
d. To assess the anti-tumor efficacy of combined therapy as determined by measurement of OS and PFS

Scientific:

a. To assess the effects of niraparib alone, and niraparib plus carboplatin on pharmacodynamic markers of DNA damage and repair, including γH2AX/RAD51 foci formation, and as measured by the PARP trapping assay
b. To explore predictive markers of response and/or resistance to therapy in serial tumor biopsy samples

8.2 Study Design

This study is a single-arm, open-label, multi-institutional Phase I dose-escalation and dose-expansion trial of the combination of niraparib and carboplatin in patients with advanced solid tumor malignancies with deleterious mutation(s) in DNA damage repair genes. The Phase Ia portion of the trial will be conducted in a 3+3 design, enrolling patients in cohorts of 3 patients each, to ensure safety and tolerability. With this design, if there are less than 2 dose-limiting toxicities (DLTs) in the first 3 patients, then 3 additional patients will be enrolled to the current dose level cohort. If there are less than 2 dose-limiting toxicities (DLTs) in these 6 patients, then 3 additional patients will be enrolled in the next dose level (Table 1), and so on. If there are greater than or equal to 2 DLTs in a given 6 patient cohort, then the dose level below will be considered the maximum tolerated dose (MTD) and will be employed as the RP2D and schedule.

Once the RP2D and schedule are identified, a Phase Ib expansion cohort of 20 additional patients will be enrolled as a pilot subgroup to determine efficacy. Of the 20 patients in this Phase Ib cohort, no more than 10 patients will have underlying breast cancer; and additionally no more than 10 patients may harbor *BRCA1* or *BRCA2* mutations.

Efficacy for both Phase Ia and Phase Ib will be assessed by radiologic assessment every 9 weeks for objective response, as well as measurement of PFS and OS. All patients meeting the eligibility criteria and who have signed a consent form, have begun treatment for at least 1 cycle of therapy, are not lost to follow-up, and are not taken off study for reasons other than progression or death will be considered evaluable for the assessment. Interim analyses to assess secondary endpoints of OS and PFS will be scheduled to occur at 12 months and 24 months.

Pharmacodynamic studies will be evaluated on participant's serial biopsy samples and serum in both portions of study, directed towards an assessment of DNA damage including γH2AX and RAD51 foci formation, as well as an assessment of PARP inhibitory activity, as measured by a PARP-trapping assay. We will also undertake a next-generation sequencing analysis of DNA repair enzymes to evaluate markers that predict response and resistance to therapy. In addition, a portion of all pre-treatment tumor samples will be used in *ex vivo* models (e.g. organoids) for further analysis of mechanism of resistance and to identify combinatorial therapies that can overcome resistance.

8.3 Sample Size Considerations

At the sites participating in this study, we anticipate being able to screen as many as 1,000 patients per year. Assuming a qualifying mutation rate of 5-10%, and 25% of screened patients being otherwise trial eligible, we anticipate enrolling 30 patients per year across multiple medical institutions within the United States. Only patients with advanced solid tumor malignancies will be eligible for enrollment. For the Phase Ia portion, there may be as few as 18 patients (6 patients at dose level 1, which proves to be too toxic, with three different schedules). The maximum number of patients (126) would occur if each schedule is employed and 6 patients are enrolled at each dose level. In the Phase Ib portion, we plan to enroll 20 patients to accelerate our understanding of the efficacy of the combination of niraparib with carboplatin, in preparation for Phase II or III study. With 20 evaluable patients in the Phase Ib portion, combined with a minimum of 18 to a maximum of 126 patients enrolled in the Phase Ia portion of the trial, there will be up to 146 patients enrolled total. At an expected accrual rate of 2-3 patients per month (roughly 30 patients per year), and an *anticipated* total patient population to meet study goals of 80 patients, the expected accrual duration will be approximately 34-38 months.

Once the RP2D and schedule are identified, a Phase Ib expansion cohort of 20 additional patients will be enrolled as a pilot subgroup to determine efficacy. Of the 20 patients in this Phase Ib cohort, no more than 10 patients will have underlying breast cancer; and additionally no more than 10 patients may harbor *BRCA1* or *BRCA2* mutations.

For the first expansion cohort, we anticipate identifying a higher number of breast cancer patients with HR deficient tumors due to frequent utilization of germline genetic testing. In order to obtain information about this combination in a variety of tumor types, we will cap the number of breast cancer patients at 10 total. Similarly, in order to obtain information in patients with a variety of defects in HR, the total number of patients with *BRCA1/2* mutations (any disease type) will also be capped at 10 total.

Enrolled patients in the Phase Ib expansion cohorts will be screened for enrollment similar to patients enrolled in the Phase Ia portion of study, and must meet the same inclusion and exclusion criteria (Appendix A). Phase Ia enrollment requirements, such as baseline imaging and consent for serial biopsies, will be upheld. Patients will then be started on treatment at the RP2D and schedule as determined during Phase Ia.

8.4 Endpoints

8.4.1 Primary Endpoints

8.4.1.1 Phase Ia Primary Endpoint

The number of grade 3 and 4 toxicities according to NCI CTCAE; Version 5.0 that occur after Cycle 1, Day 1 will be recorded at each study visit.

8.4.1.2 Phase Ib Primary Endpoint

Anti-tumor efficacy by ORR. ORR is defined as the proportion of patients whose best overall response recorded during the treatment is either CR or PR according to the RECIST v1.1.

8.4.2 Secondary Endpoints:

Clinical:

a. Median overall survival. OS is defined by time from study enrollment till death from any cause
b. Median progression free survival. PFS is defined as the time from study enrollment to determination of tumor progression by RECIST version 1.1 or death due to any cause, whichever occurs first
c. Disease control rate (DCR). DCR is defined as the proportion of patients with a documented CR, PR, or SD at 4 months according to the RECIST version 1.1

Scientific:

a. Quantification of DNA damage and repair, as measured by γH2AX/RAD51 foci formation
b. Quantification of PARP inhibition, as measured by PARP trapping assays
c. Changes in predictive markers of response and/or resistance to therapy in serial tumor biopsy samples and in *ex vivo* samples

8.5 Analysis Plan

8.5.1 Analysis for the Primary Endpoint

As a Phase I trial, statistics will be primarily descriptive. Descriptive statistics will be used to summarize patients' characteristics as well as those parameters measured in the laboratory tests. Patients' adverse events and toxicities will be tabulated according to their grades and attributions. The ORR will be estimated with its 95% exact confidence interval. In both the Phase Ia and Phase Ib portion of study, ORR will be assessed overall and by tumor subtype (breast/gynecologic, gastrointestinal [esophageal, gastric, colorectal, anal], pancreatobiliary, GU, other). The main purpose of Phase Ib is not hypothesis testing but rather observing the efficacy. However, if we observe at least 5 or more out of the 20 patients who obtain a PR, CR or SD at 9 weeks, this would be equivalent to a one-stage Phase II testing of the response rate of 0.1 vs. at least 0.3 at a 0.05 one-sided alpha level. The sample size of 20 patients would give 76% power to reject the null hypothesis of the response rate at 0.1. If, in this study, 6, 7 or 8 patients obtain a PR, CR or SD at 9 weeks, then the 80% confidence intervals for the response rates would be 16.6%-46.6%, 21.2%-51.2%, and 24.8%-56.8%, respectively.

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8.5.2 Analysis for the Secondary Endpoints

PFS and OS will be estimated using the Kaplan-Meier method. The median PFS and OS will be presented with their 95% confidence intervals if estimable. The DCR will be calculated according to RECIST v1.1 criteria, and will be compared descriptively to historical outcomes. If non-inferiority of combined therapy is observed in both portions of study as compared to historical outcomes, and combined therapy is well-tolerated, then further Phase II and/or III study will be pursued.

8.5.4 Safety Assessments

8.5.4.1 Safety Assessments

The safety of niraparib and carboplatin will be assessed by evaluating study drug exposure, adverse events, serious adverse events, oncology-related events, all deaths, as well as changes in laboratory determinations and vital sign parameters.

8.5.4.2 Duration of Study Drug

A summarization of the number of days and/or cycles subjects were exposed to study drug will be provided.

8.5.4.3 Adverse Events

Analyses of adverse events (and serious adverse events) will include only "treatment-emergent" events, *i.e.*, those that have an onset on or after the day of the first dose of study drug. Analyses will not include those that have an onset greater than 30 days after the last dose of study drug. Treatment emergent adverse events will be summarized by system organ class and preferred term according to the MedDRA adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given severity, NCI CTCAE toxicity grade, and relationship to study drug will be provided.

8.5.4.4 Deaths

The number of subject deaths will be summarized (1) for deaths occurring while the subject was still receiving study drug in this study, (2) for deaths occurring off treatment within 30 days after the last dose of study drug, and (3) for all deaths in this study regardless of the number of days after the last dose of study drug. The relatedness of the deaths to the study drugs will also be provided.

9.0 CORRELATIVE RESEARCH AND TUMOR SAMPLE MANAGEMENT

The premise that underlies the use of this combination is that niraparib plus carboplatin will induce significant DNA damage, and that tumors with evidence of HRD will be particularly dependent upon PARP activity to recover from the carboplatin-induced DNA damage. Thus, concurrent inhibition of PARP will result in overwhelming DNA damage in cancer cells, ultimately leading to increased cancer cell death. It is therefore possible that tumors that exhibit these deficiencies will be particularly sensitive to DNA damage and PARP inhibition, which may predict an increased ORR with therapy. To assess this hypothesis – that increased DNA damage due to anti-cancer therapy may lead to increased ORR – we will perform correlative analyses to quantify DNA damage by measurement of γH2AX and RAD51 foci formation in patient tumor samples. All patients will undergo serial, fresh tumor biopsies to carry out these assessments, as outlined in Figures 1-3.

Furthermore, we would presume that tumors that are resistant to this combination would have lower PARP or DNA repair gene expression levels, and/or no induction of gene expression upon treatment. To monitor for the development of resistance to therapy, a portion of all pre-treatment tumor samples will be used in *ex vivo* models (e.g. organoids) for further analysis of mechanism of resistance and to identify combinatorial therapies that can overcome resistance. Additionally, we will assess ongoing PARP inhibitor activity as measured by a PARP-trapping assay on each tumor biopsy sample.

Finally, serial blood samples for patients will be collected prior to treatment on D1 of each cycle for additional correlative study by Caris Life Sciences and Dr. Brody's lab.

9.1 Sample Labeling Overview

Patients will be de-identified and labeled with a 12 character study label (XX-X-X-XXXXXX):

- The first two characters will be the patient's initials
- The third character will be the site number from which the patient was enrolled (single digit)
    - 1 = Georgetown
    - 2 = Yale
    - 3 = Hackensack
    - 4 =Levine
    - 5 = John's Hopkins
    - 6 = Vanderbilt
    - 7 = Other
- The fourth and fifth characters will be the patient study number (e.g. 01, 02, 03, etc.)
- The sixth character will be the timing of collection
    - 1 = First biopsy/sample
    - 2 = Second biopsy/sample
    - 3 = Third biopsy/sample
    - 4 = Fourth biopsy/sample at Final Off Study Visit or at progression
    - 5 = Serum collection
- The final characters will be the date in MM/DD/YR format

9.2 Timing and Utilization of Tumor Biopsies

For each biopsy, 5 individual cores will be obtained with an 18-20 gauge needle. The utilization of the cores differs depending upon which biopsy is being obtained. Please refer to Section 4.3.2 and the Lab Manual for details

Shipping details and addresses are all summarized in Appendix D.

Pre-Treatment Biopsy

Following successful screening and enrollment of patients with advanced solid tumor malignancy and known deleterious mutations in selected DNA repair genes, a pre-treatment tumor biopsy will be obtained (within 4 weeks of Day 1 of study treatment).

Second & Third Biopsies (For patients in the Phase Ib portion)
Second and third biopsies will be obtained as outlined in Figures 1-3. The second biopsy will occur on C1D14 (range C1D10-14) in schedule #1 (timing of biopsy in alternative schedules will differ), on niraparib therapy alone. The third biopsy will occur on C2D14 (rabge C2D10-14), on niraparib and carboplatin therapy. ***There can be some flexibility with the timing of the biopsies, but it is important that the second and third biopsies take place on a day that the patient received a dose of niraparib.***

Biopsy Upon Progression (For patients in the Phase Ib portion)
All patients whose disease has NOT rapidly progressed on trial will undergo a biopsy upon disease progression for ongoing correlative studies. Specifically, patients who meet the following conditions will have a biopsy upon progression:

- The patient experiences a RECIST 1.1 confirmed partial or complete response at any point, and then subsequently experiences disease progression
  Or
  The patient experiences stable disease of 27 weeks (to comport with the timing of restaging imaging), and then subsequently experiences disease progression

9.3 Correlates

9.3.1 RAD51 Foci Formation

9.3.1.1 Background

RAD51 is a protein that assists in repair of DNA DSBs, particularly in homologous recombination of DNA during DSB repair. Further, RAD51 allows for DNA strand transfer between a damaged sequence and its undamaged homologue. RAD51 is particularly important in HRD tumors, as tumors with previously defined HRD status are unable to induce RAD51 foci on DNA damage[109-110]. As such, HRD tumors tend to have low levels of quantifiable RAD51 foci formation. In this portion of correlative study, we will measure RAD51 foci formation by immunofluorescence to not only attempt to quantify DNA damage following combined treatment with niraparib plus carboplatin, but also to determine if lower levels of RAD51 foci formation are seen in a variety of subtypes of HRD tumors.

9.3.1.2 Methodology for RAD51 Foci Formation Immunofluorescence

Tumor samples will be tested in Dr. Brody's lab at OHSU, who will perform RAD51 foci formation immunofluorescence as outlined below:
Growing and fixing the cells:

1. *Plating*: Prior to plating cells, cover slips are sterilized by soaking in methanol or 70% ethanol for 10-15 minutes, washed at least 2X with sterile PBS and treated with histogrip. Plate $5x10^4$ cells (or fewer depending on cell type and length of culture time)· overnight on three sterile cover slips per condition in 12-well dishes (Fisher 12-546 18CIR-2). Cells should be in log phase growth and not likely to be confluent by the end of treatment as confluency can affect the DNA damage repair response.
2. Treat cells as desired.
3. *PBS Wash*: At the appropriate endpoint, place cells on ice, aspirate media, and wash with 2ml cold PBS twice with 10m incubation in between.
4. *Fixing*: Add 1.0 ml cold paraformaldehyde solution for 15m (keep cells on ice and protected from light)
5. Remove paraformaldehyde solution and wash with 2 ml PBS for 10m. Aspirate PBS.
6. Add 1.5 ml cold PBS, cover, and store at 4°C. (up to a month).
7. *Permeabilization*: Aspirate PBS and add 1mL of 0.5% triton into each well for 10 minutes.
8. After a PBS wash, incubate with 1mL BSA blocking buffer for 30 minutes at RT on a shaker. After the 30 min blocking buffer step, rinse with 1mL PBS per well.
9. *Staining*: Prepare the 1° antibody in BSA blocking buffer (GeneTex at 1:500 dilution). After blocking rinse well with PBS and incubate with 1° antibody dilution on shaker for 1 hour. Protect from light.
10. Wash twice with PBS for 10 minutes each.
11. Prepare the LIGHT SENSITIVE 2° antibody dilution (Red anti mouse 594; Alexa Fluor A11005 antibody at 1:2000 dilution in BSA blocking buffer.
12. After two PBS washes, add 0.4mL of prepared 2° antibody on each cover slip and incubate in dark for 30 minutes.
13. Aspirate 2° antibody dilution and wash cover slips twice with 1 mL PBS, 10 minutes each.

14. Mount coverslips on slides with mounting media ProlongGold containing DAPI . Let dry overnight at room temperature and protected from light.
15. Store in slide box at 4°C until imaging.

9.3.1.3 Data Collection

Testing will be done in a patient DE-IDENTIFIED manner. The de-identified data report, linked with a patient study number, will be entered into the study database in a CRF designed to capture the results.

9.3.1.4 Statistical Analyses

Fisher's exact tests will be used to compare the level of pharmacodynamic activity among cohorts and treatment schedules, as well as to compare any differences in the anti-tumor efficacy among cohorts, treatment schedules and pharmacodynamic activity profiles.

9.3.2 γH2AX Foci Formation

9.3.2.1 Background

H2AX is a member of the histone H2A family, and is involved in organizing DNA into chromatin. H2AX phosphorylation at serine-139 (γH2AX) is an established, sensitive marker of DSBs[111]. More specifically, H2AX is a key component in DNA repair, becoming rapidly phosphorylated from the carboxyl terminus to form γH2AX at DSB sites, and generating a focus at the DSB where other proteins involved in DNA repair and chromatin remodeling accumulate[112-113]. Because many cancer treatments induce DSBs, γH2AX quantification serves as a measure of treatment effect. As such, measurement of γH2AX foci formation by immunofluorescence foci imaging and counting will be used in this study to quantify DNA damage following combined treatment with niraparib plus carboplatin, and to determine if higher levels of γH2AX are associated with improved treatment efficacy.

9.3.2.2 Methodology for γH2AX Foci Formation Immunofluorescence

Tumor samples will be tested in Dr. Brody's lab at OHSU, who will perform γH2AX foci formation immunofluorescence as outlined below:

1. Seed cells in 6-well dishes on cover slips for treatments.
2. After treatment, remove culture media and gently wash cells twice with 1x PBS.
3. Fix cells with 3.7% Formaldehyde in 1X PBS at room-temp for 10 minutes.
4. Rinse cells twice with 1X PBS (can be stored in 1X PBS @ 4°C for several weeks).
5. Permeabilize cells with 0.3% TritonX (diluted in 1X PBS) for 30 min at 37C.
6. Incubate cells with primary antibody (Millipore mouse monoclonal (Ser139) (Cat# 05-636), typically 1:500) in 5% BSA blocking buffer for 1 hour at room temp (or overnight at 4°C).
7. Wash cells twice with 1X PBS, 10minutes each.
8. Incubate cells with secondary antibody (Alexafluor 488 anti-mouse, typically 1:1000) in 5% BSA blocking buffer for 1 hour at RT.
9. Wash twice with 1X PBS.
10. Mount coverslips on slides with mounting media ProlongGold containing DAPI. Let dry overnight at RT and protected from light.
11. Store in slide box at 4°C until imaging.

9.3.2.3 Data Collection

Testing will be done in a patient DE-IDENTIFIED manner. The de-identified data report, linked with a patient study number, will be entered into the study database in a CRF designed to capture the results.

9.3.2.4 Statistical Analyses

Fisher's exact tests will be used to compare the level of pharmacodynamic activity among cohorts and treatment schedules, as well as to compare any differences in the anti-tumor efficacy among cohorts, treatment schedules and pharmacodynamic activity profiles.

9.3.3 PARP Trapping Assay

9.3.3.1 Background

Critical in determining the anti-tumor efficacy of PARP-inhibitor therapy is applying a validated method to measure PARP activity within a tumor sample. For this portion of correlative study, PARP-inhibitor activity will be measured by cellular fractionation and PARP trapping in chromatin bound fraction (immunoblots), as well as assessing PARP inhibitor efficacy by PARP assays quantifying Relative PARylation through ELISA and immunoblots.

9.3.3.2 Preliminary Methodology for PARP Trapping Assay

Tumor samples will be assayed using an enzyme-linked immunosorbent assay (ELISA, Trevigen, as per manufacturer's instructions) to evaluate potency of PARP inhibition.

Tumor samples will be tested for PARP inhibitor activity by Dr. Brody's lab at OHSU by PARP trapping assay as outlined below:

1. Cells are harvested and washed three times with ice-cold PBS, and pelleted by quick spinning at 1,000 rpm for 1 to 2 min.
2. Soluble proteins are then extracted with ice-cold 0.1% Triton X-100 in CSK buffer for 20 min at 4°C.
3. The insoluble, chromatin-bound fraction was then pelleted by low-speed centrifugation at 3,000 rpm for 5 min at 4°C.
4. These pellets are then re-extracted by incubating in CSK buffer and collected by centrifugation at 3,000 rpm for 10 min at 4°C.
5. The final pellet fraction (containing chromatin-bound proteins) or total cell pellets are solubilized in radioimmunoprecipitation assay (RIPA) buffer and equal protein is resolved by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE). Histone H3 and GAPDH will be used as positive controls for validating chromatin- bound and soluble protein fractions respectively. Trapped PARP1 will be normalized and quantified by Licor densitometry.
6. Additional updates to PARP Assay methodology section to come as lab performing this portion of correlative study finalizes protocol(s).

9.3.3.3 Data Collection

Testing will be done in a patient DE-IDENTIFIED manner. The de-identified data report, linked with a patient study number, will be entered into the study database in a CRF designed to capture the results.

9.3.3.4 Statistical Analyses

Fisher's exact tests will be used to compare the level of pharmacodynamic activity among cohorts and treatment schedules, as well as to compare any differences in the anti-tumor efficacy among cohorts, treatment schedules and pharmacodynamic activity profiles.

9.3.4 Resistance Mechanisms

Serial tumor biopsies will be prepared for *ex vivo* analyses to monitor the development of mechanisms of resistance to either PARP-inhibitor or carboplatin therapies. Tumor samples will be placed in a pre-provided Eppendorf tube with collection media and shipped on ice to Dr. Brody's lab at OHSU. Cancer-derived organoids have been shown *in vitro* to retain the same complex, heterogeneity of genetic alterations present *in vivo* in a given patient's tumor. As such, organoids are an ideal medium for exploration of the development of resistance mechanisms in cancer tissues following the initiation of anti-cancer therapy, with new mutations identified likely playing a role in the development of resistance to therapy. The specific genetic alterations leading to PARP-inhibitor resistance are unknown, and we hope to add significant framework to this discussion with our correlative analysis as outlined.

9.3.5 Additional Correlates

During the course therapy, patients will also undergo blood sample collection for additional correlative analyses:

- Patients will submit a 10mL sample of blood in a red top heparinized tube for future research at the time of first biopsy, Cycle 1 Day 1, and every 3 weeks until progression. These samples will be processed to isolate serum, which will be batched and shipped to Dr. Brody's lab at OHSU.

10.0 ETHICAL CONSIDERATIONS

10.1 Institutional Review Board (IRB)

GCP requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB. IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to the IRB. During the conduct of the study, the investigator should promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

10.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

10.3 Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Each informed consent will be reviewed, signed and dated by the subject and the person who administered the informed consent. A copy of each informed consent will be given to the subject and each original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Tissue sample collection for analysis will only be performed if the subject has voluntarily consented to participate after the nature of the testing has been explained and the subject has had the opportunity to ask questions. If the subject does not consent to the tissue sample collection, it will not impact the subject's participation in the study.

10.4 Ethical Consideration for Enrollment

Only patients with advanced cancer, for whom no curative therapy exists, will be considered for enrollment. The only treatment options for these patients are conventional chemotherapy, radiation, or participation in a clinical trial. As described above, the combination of niraparib and carboplatin is a rational and promising combination for such patients.

10.5 Protection of Patient Confidentiality

All patient records, questionnaires, and tissue specimens will be de-identified using a letter and number assigned to their case at the time of enrollment on study. No record or specimen will contain information which could identify the patient. The key which connects patient identifiable information with this assigned number will be held by the Principal investigator. For computer records, the key will be protected by a double password protection system. Any paper records will be contained in a locked cabinet within a locked office to ensure patient’s privacy is protected.

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APPENDIX A: STUDY ELIGIBILITY CHECKLIST

Niraparib Plus Carboplatin in Patients with Homologous Recombination Deficient Advanced Solid Tumor Malignancies

Study ID: _____

Instructions: This form should be completed by the research staff before registering the patient into the trial.
Completed form should be scanned/emailed to [redacted]

☐ Georgetown University Medical Center ☐ Other Institution _____

Inclusion Criteria	Yes	No	NA
3.2.1 Patients PRE-identified as having either a germline deleterious mutation or tumor expression of a deleterious mutation) as determined by Next-generation DNA sequencing only, in at least one gene involved in DNA damage repair through homologous recombination including but not limited to: RAD50/51/51B, BARD1, BLM, BRCA1, BRCA2, BRIP1, FANCA/C/D2/E/F/G/L, PALB2, or BAP1. 3.2.1.1 Patients with **somatic mutations** will be PRE-identified as having a homologous recombination mutation based on NGS done in a CLIA certified, CAP tested and bioinformatics-validated testing lab PRIOR to enrollment in this current protocol. The testing may have been done at any time prior to enrollment. 3.2.1.1.a The determination of a deleterious mutation must be supported in the documentation included in the testing, and should include clinical, or pre-clinical literature to support the finding that a specific mutation results in impaired function of the gene, and thus impaired DNA repair through homologous recombination. Variants of unknown significance will not be eligible. 3.2.1.1.b For the Phase Ib portion of the study, if any patient has had NGS testing more than 12 months prior to enrollment, then a repeat NGS test must be done and the deleterious somatic mutation must be re-identified for inclusion. 3.2.1.2 Patients with **germline deleterious mutations** may have been identified at any time point prior to inclusion in the protocol and do NOT need to have this genetic testing repeated regardless of time frame and intervening therapy.			
Advanced, solid tumor malignancy (other than prostate cancer, see Section 3.3.11). 3.2.2.1 The tumor must be amenable to biopsy. 3.2.2.2 For the Phase Ib portion, the patient must consent to 4 mandatory biopsies during study. **Note:** *If there are any issues with obtaining the study required pre-treatment biopsy (ie. it is deemed unsafe to obtain the biopsy or it is determined that the initial biopsy sample obtained did not contain tumor tissue), the subject may only be allowed to enroll after receiving permission from the Study Chair(s). Additionally, they will be exempt from being required to obtain additional on study biopsies.*			
3.2.3 Life expectancy of more than 3 months			
3.2.4 Age ≥ 18 years			
3.2.5 Measurable disease by RECIST v1.1 criteria (tumor ≥ 1 cm in longest diameter on axial image on computed tomography (CT) or magnetic resonance imaging (MRI) and/or lymph node(s) ≥ 1.5 cm in short axis on CT or MRI) on baseline imaging			
3.2.6 ECOG performance status (PS) of 0 to 1 (Table 11, Appendix A)			
3.2.7 Patients who have received and experienced disease progression on, or have been intolerant to, standard first line therapies known to confer clinical benefit. Patients who refuse standard therapy would also be eligible, as long as their refusal is documented.			

Inclusion Criteria	Yes	No	NA
3.2.8 Adequate hepatic, bone marrow, and renal function at the time of enrollment: **3.2.8.1 Bone Marrow**: Absolute neutrophil count (ANC) ≥ 1,500/mm3; Platelets ≥ 100,000/mm3; Hemoglobin ≥ 9.0 g/dL. Patients must be able to meet the criteria without transfusion within 4 weeks or receipt of colony stimulating factors, filgrastim (eg neupogen or biosimilar) within 14 days, or peg-filgrastim (eg, neulasta) or recombinant erythropoietin within 4 weeks before obtaining sample			
3.2.8.2 Renal function: Serum creatinine ≤ 2.0 mg/dL OR creatinine clearance ≥ 50 mL/min/1.73 m2			
3.2.8.3 Hepatic function: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × the upper normal limit of institution's normal range. Total bilirubin ≤ 1.5 × the upper normal limit of institution's normal range. For subjects with liver metastases, AST and ALT < 5 × the upper normal limit of institution's normal range, and total bilirubin >1.5 - 3.0 x the upper normal limit of institution's normal range are acceptable as long as there is no persistent nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia			
3.2.8.4 Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) must be ≤ 2 X the upper limit of the institution's normal range and International Normalized Ratio (INR) < 2. Subjects on anticoagulation (such as coumadin) will be permitted to enroll as long as the INR is in the acceptable therapeutic range as determined by the investigator			
3.2.9 Patients may have received an unlimited number of prior therapies. Prior anti-cancer therapies must be given ≥ 2 weeks prior to Cycle 1, Day 1 on trial (and the patient must have recovered from all side effects of prior therapies that are exclusionary, as per Section 3.3 below)			
3.2.10 Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring conscious sedation such as endoscopies or mediport placement may only require a 24-hour waiting period, but this must be discussed with an investigator			
3.2.11 Female patient has a negative serum or urine pregnancy test within 72 hours prior to taking study treatment if of childbearing potential and agrees to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment, or is of non-childbearing potential.			
Non-childbearing potential is defined as follows (by other than medical reasons): • ≥45 years of age and has not had menses for >1 year • Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation • Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure Otherwise the patient must be willing to employ methods to avoid pregnancy. Abstinence is an acceptable method to avoid pregnancy if this is the established and preferred method for the patient. Alternatively, the patient and partner must use 2 adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. Information must be captured appropriately within the site's source documents.			
Male patients must also agree to use an adequate method to avoid pregnancy, which may include abstinence, if this is the established and preferred method for the patient starting with the first dose of study treatment through 180 days after the last dose of study treatment.			
Additionally, the participants must agree to not breastfeed during the study or for 180 days after the last dose of study treatment.			

Inclusion Criteria	Yes	No	NA
3.2.12 Patient is capable of swallowing pills whole			
3.2.13 Subject is capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the IRB, prior to the initiation of any screening or study-specific procedures			
Exclusion Criteria	**Yes**	**No**	**NA**
3.3.1 Prior disease progression while receiving platinum chemotherapy; or any platinum chemotherapy within the last 6 months 3.3.1.1 For all patients (except breast cancer patients) who received platinum-based adjuvant or neo-adjuvant chemotherapy, at least 6 months must have passed between the last dose of platinum-based therapy and the development of metastatic disease. 3.3.1.2 For breast cancer patients, at least 12 months must have passed between the last dose of platinum-based adjuvant or neo-adjuvant therapy and the development of metastatic disease			
3.3.2 Patients must not require "support" to maintain adequate blood counts, as defined by: 3.3.2.1 Patients must not have received a transfusion (platelets or red blood cells) ≤ 4 weeks prior to initiating protocol therapy. 3.3.1.2 Patient must not have received colony stimulating factors, filgrastim (eg neupogen or biosimilar) within 14 days, or peg-filgrastim (eg, neulasta) or recombinant erythropoietin within 4 weeks prior initiating protocol therapy. 3.3.2.1 Participant has had any known Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment.			
3.3.4 Known or suspected CNS metastases, unless at least one month has passed since last local CNS therapy and there is no evidence for recurrent or progressive CNS disease on follow up imaging. Participants may remain on steroids for CNS disease if they are taking a stable dose			
3.3.5 Active severe infection, or known chronic infection with HIV or hepatitis B virus (testing not required prior to enrollment) 3.3.5.1 Patients with chronic Hepatitis C virus may be enrolled if there is no clinical/laboratory evidence of cirrhosis AND the patient's liver function tests fall within the parameters set in Section 3.2.8.3, Inclusion Criteria, Hepatic function			
3.3.6 Cardiovascular disease problems including unstable angina, therapy for life-threatening ventricular arrhythmia, or myocardial infarction, stroke, or congestive heart failure within the last 6 months.			
3.3.7 Life-threatening visceral disease or other severe concurrent disease that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.)			
3.3.8 Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)			
3.3.9 Presence of a psychiatric illness or social situation that would limit compliance with study requirements			
3.3.10 Women who are pregnant or breastfeeding			
3.3.11 The subject must not have had diagnosis, detection, or treatment of another type of cancer ≤2 years prior to randomization (except basal or squamous cell carcinoma of the skin that has been definitively treated). Questions regarding the inclusion of individual subjects should be directed to the Principal Investigator, Dr. Isaacs.			

Exclusion Criteria	Yes	No	NA
3.3.12 Due to licensing agreements for Niraparib, patients with a current diagnosis of prostate cancer will be excluded.			
3.3.13 Clinically significant peripheral neuropathy at the time of enrollment (defined in the NCI CTCAE v4.0) as grade 2 or greater neurosensory or neuromotor toxicity)			
3.3.14 Patients must not have had investigational therapy administered ≤4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study			
3.3.15 Patients must not have had radiotherapy encompassing >20% of the bone marrow within 2 weeks; or any radiation therapy within 1 week prior to Day 1 of protocol therapy			
3.3.16 Patients must not have a known hypersensitivity to the components of niraparib or the excipients			
3.3.17 Patients must not have current evidence of any condition, therapy, or laboratory abnormality (including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]) that might confound the results of the study or interfere with the patient's participation for the full duration of the study treatment or that makes it not in the best interest of the patient to participate			
3.3.18 Patients must not be considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent			
3.3.19 Patient must not have any known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)			

INVESTIGATOR SIGNATURE:_____**Date:**_____

STUDY COORDINATOR SIGNATURE:_____**Date:**_____

Table 11: ECOG Performance Status Scale

Grade	ECOG
0	Fully Active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX B: PATIENT REGISTRATION FORM

Niraparib Plus Carboplatin in Patients with Homologous Recombination Deficient Advanced Solid Tumor Malignancies

Study ID: _____
Instructions: This form should be completed by the research staff before registering the patient into the trial.
Completed form can be scanned/emailed to [redacted]

☐ Georgetown University Medical Center

☐ Other Institution _____

☐ Treating Physician _____ _____

1. Date Informed Consent signed: ____/____/___

2. Screening Date: ____/____/___

3. Start date for treatment: ____/____/_____

4. Prior therapies (date initiated/type):

5. Please fax the following documentation:
   - ☐ Pathology Report
   - ☐ Physicians Note validating:
   - ☐ Previous treatments
   - ☐ CT showing RECIST criteria
   - ☐ Laboratory Results
   - ☐ Past Medical History

APPENDIX C: Data Sharing Plan

Data sharing for this study will be conducted in compliance with the February 26, 2003 NIH Statement on Data Sharing (NOTICE: NOT-OD-03-032). The collaborating sites for this study generate a wide variety of scientific and clinical data and Data Sharing and Archiving will be handled by in accordance with NIH Statement on Data sharing, institutional internal document retention policies and all application rules, regulations and statutes. Subject to institutional policies, local IRB guidelines, and local, state and Federal laws and regulations including the Privacy Rule and the Bayh-Dole Act, we will make finished research data available through scientific presentations, publications (paper, web and other), depositing gene sequence, gene expression and other data in searchable electronic repositories, attendance at scientific meetings and extending invitations to scientists from other institutions for discussion. In accordance with the NIH policy, such data shall be made widely and freely available while safeguarding the privacy of participants and protecting Lombardi's confidential and proprietary data.

The participating sites will maintain awareness, and may participate in, discussions between members of multiple scientific and technical disciplines and their professional societies concerning data sharing, standards and best practices, and to create an environment that supports and develops data sharing tools. We will participate in or make ourselves aware of the outcome of any workshops the NIH or AACR will convene to address data sharing and which may address areas such as cleaning and formatting data, writing documentation, redacting data to protect subjects' identities and proprietary information, and estimating costs to prepare documentation and data for sharing.

The NIH has recognized the need to protect patentable and other proprietary data and notes the restrictions on the sharing of data that may be imposed by agreements with third parties. Under the Bayh-Dole Act, grantees have the right to elect and retain title to subject inventions developed with Federal funding, and further, to commercialize any invention to which they retain title. Since its is not the stated intent of the NIH statement on Data Sharing to discourage, impede or prohibit the development of commercial products from federally funded research, our collaborating sites will continue to perform inventive activities, to seek patent protection for inventions that relate to data generated and may choose to defer publication or enter into agreements with third parties that may result in certain restrictions on data sharing. We note that seeking patent protection results in publication of the patent application into the public domain and, thus, may result in the data being broadly disseminated.

All specimens submitted to any of the shared resource laboratories will be bar-coded upon receipt and assigned a unique identifier using a common software program. Tracking of specimens and their utilization will be carried out using a web-based system that will represent a modification of the systems presently in place at Georgetown (including but not limited to G-DOC, Georgetown Database of Cancer, Medidata Rave, REDCap), which will also give us the ability to track sample utilization. These systems have an "honest broker" interface which ensures HIPPA compliance and protection of any human subjects. As the same sample may well be used for genomic, proteomic, histopathological and clinical interrogation, assignment of a unique identifier as well as a common administrative structure ensures efficient cross-database interrogation.

Data security

The rights and privacy of people who participate in sponsored clinical research will be protected at all times. In the event that data is intended for broader use, it will be de-identified and would not permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects. No efforts will be made to identify individual cases, and any shared archive data will not be linked to other identifiable data. The following de-identification and security procedures will be followed to share information with collaborators part of the study:

1) Deletion of 18 HIPAA identifiers
    a. Non-identifiable unique patient ID will be generated in G-DOC
2) Secure netID-based single sign-on (netID is Georgetown's LDAP based secure login system)
3) Users will have to *authenticate* themselves prior to accessing controlled data
4) Furthermore, based on their roles, users will require *authorization* to see specific studies

5) Auditing and security assessments will be performed on a quarterly basis to ensure appropriate de-identification procedures and use of data.

For future studies involving new data types that are not covered in the descriptions above, NIH policy on data sharing will be followed where applicable. For example, Genome Wide Association Studies, if conducted, will comply with *NIH Guidelines* NOT-OD-07-088 (http://grants.nih.gov/grants/gwas/) for data release. Following these guidelines, GWAS data will be submitted to NCBI's dbGAP (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap) or other tools as the NIH's policy on GWAS evolves.

Data Disclosure

GUMC (Georgetown University Medical Center) has a Confidentiality and Non-Disclosure policy that pertains only to proprietary information belonging to GUMC. The disclosure of research information such as microarray analysis results is at the discretion of the faculty and staff. Notably, investigators with NIH funding are expected to make their data and results public in a reasonable time frame (Please see the University plan for sharing and distributing biomedical research resources at http://otc.georgetown.edu/documents/inventors/NIHGrantLetter_ModelOrganismsUpdate_6-27-05.doc . To protect institutional intellectual property, the institution does have an internal review process prior to submission of journal manuscripts. This process will be propagated to other study sites as well.

APPENDIX D: Sample Shipment Addresses

Please refer to the Lab manual for current Shipment Addresses

Formalin-Fixed Tumor Biopsies
- Samples will be placed in an institution-supplied formalin vial, and shipped to:
- Dr. Jonathan Brody (Clinical trial samples, Immediate attention)

Ex vivo model Tumor Biopsy Sample(s)
- Biopsy samples collected for Ex vivo models will be collected in pre-supplied Eppendorf tubes containing collection media and will be shipped overnight on ice to:
- Dr. Jonathan Brody (Clinical trial samples, Immediate attention)

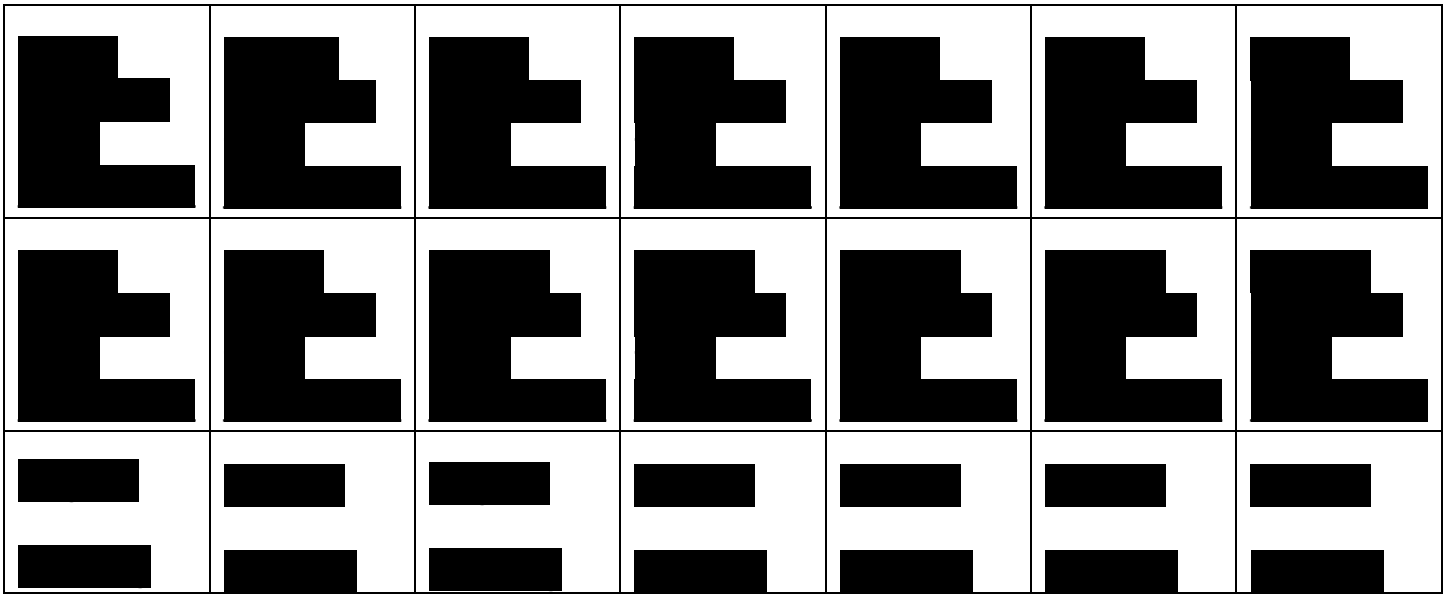
Brody Lab Blood Collection for Correlative Study
- Samples will be collected in institution-supplied red top tubes, serum isolated, and sent frozen in batches to:
- Dr. Jonathan Brody (Clinical trial samples, Immediate attention)

Extra Cores
- Core biopsy sample(s) that are collected to be held in reserve should be placed in a standard formalin vial and submitted to surgical pathology for paraffin embedding. The sample(s) from this(these) FFPE block ***should not be cut*** for an H&E analysis. Rather, the block(s) will be requested from surgical pathology, and sent to:
- Dr. Jonathan Brody (Clinical trial samples, Immediate attention)

APPENDIX E – PATIENT DRUG DIARY

PATIENT INITIALS AND STUDY NUMBER _____

Cycle Number: _____ Day 1 Date: ___/____/_____



* Treatment with Carboplatin, starting Cycle 2

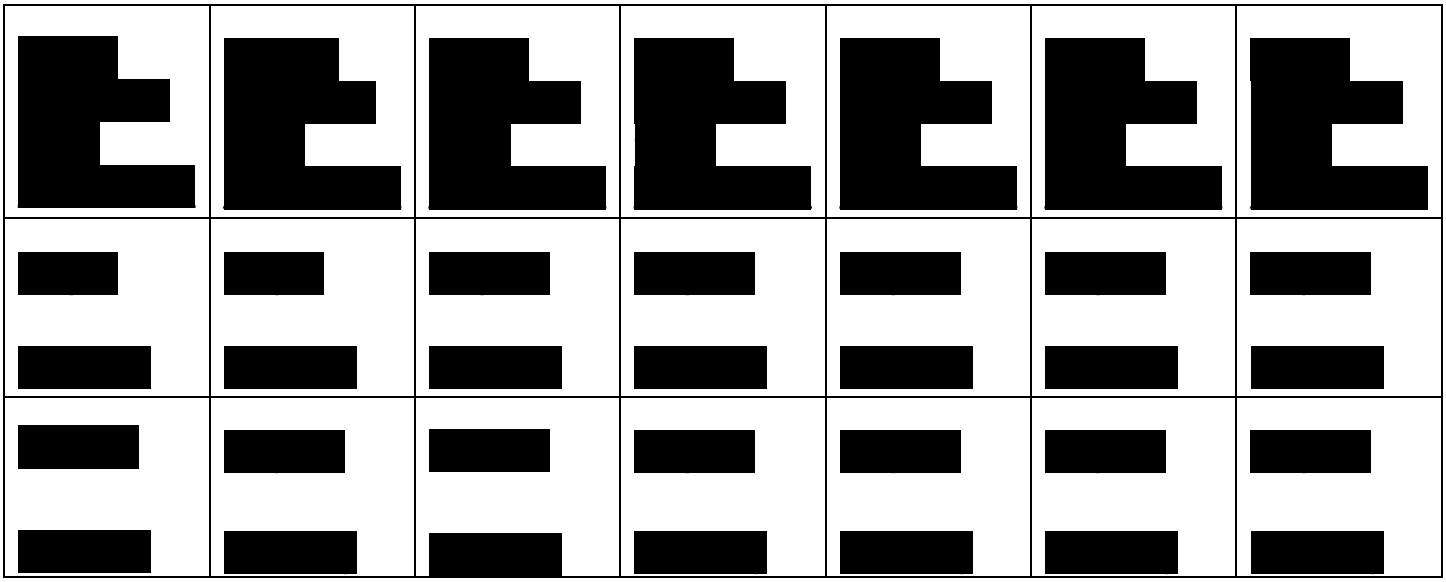
Instructions:

- Record the date and time that you took your Niraparib dose
- Take with a large glass of water (~250 mL) at the same time each day, with or without food
- Swallow whole without crushing, chewing, or opening the pills
- If vomiting occurs, do not take another dose.
- If dose is not taken within 6 hours of the intended time, the dose should be skipped and not replaced or made up on a subsequent day.
- Store niraparib at room temperature.
- Bring your bottles of niraparib (empty, partially filled, or full) and this diary to your next appointment.

Alternative Dose Schedule (Schedule #2)

PATIENT INITIALS AND STUDY NUMBER _____

Cycle Number: _____ Day 1 Date: ___/____/_____



* Treatment with Carboplatin, starting Cycle 2

Instructions:

- Record the date and time that you took your Niraparib dose
- Take with a large glass of water (~250 mL) at the same time each day, with or without food
- Swallow whole without crushing, chewing, or opening the pills
- If vomiting occurs, do not take another dose.
- If dose is not taken within 6 hours of the intended time, the dose should be skipped and not replaced or made up on a subsequent day.
- Store niraparib at room temperature.
- Bring your bottles of niraparib (empty, partially filled, or full) and this diary to your next appointment.

Alternative Dose Schedule (Schedule #3)

PATIENT INITIALS AND STUDY NUMBER _____

Cycle Number: _____ Day 1 Date: ___/____/_____

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Treatment with Carboplatin, starting Cycle

Instructions:

- Record the date and time that you took your Niraparib dose
- Take with a large glass of water (~250 mL) at the same time each day, with or without food
- Swallow whole without crushing, chewing, or opening the pills
- If vomiting occurs, do not take another dose.
- If dose is not taken within 6 hours of the intended time, the dose should be skipped and not replaced or made up on a subsequent day.
- Store niraparib at room temperature.
- Bring your bottles of niraparib (empty, partially filled, or full) and this diary to your next appointment.

Appendix F– Safety Reporting Information

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 Institution or qualified designee to GSK within 1 working day of first becoming aware of the possible defect to GSK QA at [redacted]. 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.

Reporting Adverse Events

Recording of Adverse Events

Adverse events (AEs) will be collected from the first dose of drug name to 30 days after last study drug administration. Each AE will be assessed by the investigator for seriousness, causality, and severity.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. For the purposes of this study, causality should be assessed for each study drug as Yes/No.

Severity should be assessed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v.5)

Serious Adverse Events (SAEs)

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening - This means that the patient is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization - Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE. Planned hospitalizations should be captured in medical history.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s) - An important medical event may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

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.

Adverse Events of Special Interest
The Adverse Events of Special Interest (AESIs) for this study are myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). AESIs must be reported to the Institution as soon as the Investigator becomes aware of them.

Pregnancy
Pregnancies (and pregnancy outcomes) occurring in a female patient or a female partner of a male patient must be reported to the Institution.
Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Spontaneous abortions should always be reported as SAEs.
The Investigator should follow-up with the study patient or the female partner of the study patient until delivery or termination of pregnancy, even if the patient was withdrawn from the clinical study or the clinical study was completed. GSK will be informed of all pregnancy outcomes.

Reporting to Sponsor
Investigators must report to the Institution any SAE, AESI or pregnancy occurring from the first dose of drug name to 30 days after last study drug administration. Serious adverse events occurring after this 30 day period and coming to the attention of the Investigator must be reported only if they are considered causally-related to the study drug. All events should be reported within 24 hours of becoming aware of the event.

Institution AE and Pregnancy Reporting Information
Email to the LCCC Consortium IIT Office and to Dr. Isaacs [redacted] to confirm receipt of those records.

Reporting to GSK
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.

GSK SAE, AESI, and Pregnancy Reporting Information
Email: [redacted] Fax: [redacted]

On a monthly basis, Sponsor will forward a line listing of all events that have been reported to date. 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. GSK's practice is to acknowledge receipt of all safety information with 72 hours. Institution should resend any materials that are not acknowledged within this time period.

Follow-up of Adverse Events
All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

SUSAR Distribution
A central contact at the Sponsor will forward any SUSARs which have occurred on other trials that involve the use of GSK's Investigational Product for the duration of this study.

Investigational Product
The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

Dispensing
The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Investigator Agreement or their qualified designees. The investigator, sub-investigators, or qualified designees also agree that the study drug(s) will be dispensed only to study subjects who have provided written informed consent and have met all entry criteria and in accordance with the instructions provided in the pharmacy manual.

Drug Accountability
The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatment throughout the clinical study. The study treatment accountability log includes information including the enrollment number, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as 'returned' and kept separate from the products not yet dispensed.

All dispensing and accountability records should be stored in accordance to the Sponsor-Investigator's directions. The pharmacist will dispense study treatment for each patient according to the protocol and Pharmacy Manual, if applicable.