A Phase II Study Evaluating Safety and Efficacy of Niraparib in Patients with Previously Treated Homologous Recombination (HR) Defective or Loss of Heterozygosity (LOH) high Metastatic Esophageal/Gastroesophageal Junction/Proximal Gastric Adenocarcinoma

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 01SEP2021

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

_____ _____
Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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Location of Facility (City and State)

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SYNOPSIS

TITLE	A Phase II Study Evaluating Safety and Efficacy of Niraparib in Patients with Previously Treated Homologous Recombination (HR) Defective or Loss of Heterozygosity (LOH) high Metastatic Esophageal / Gastroesophageal Junction/ Proximal Gastric Adenocarcinoma
PHASE	II
OBJECTIVES	Primary Objective: Determine objective response rate (ORR) with niraparib in patients with metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma previously treated with platinum containing chemotherapy and harboring high genome wide loss of heterozygosity (LOH) or defective homologous recombination noted through deleterious alterations in HR genes. Genes analyzed will include: BRCA1/2, PALB2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, NBN, ARID1A and GEN1. Patients can have somatic and/ or germline mutations. Deleterious mutations in HR genes are defined as those that have been previously characterized to be loss-of-function/pathogenic/or likely pathogenic as specified per the following databases: Clinvar, OncoKB, or BRCAExchange. Mutations or small insertions or deletions that results in truncation, frameshift, stop codon loss, or stop codon gain will also be considered deleterious irrespective of their presence in the aforementioned databases unless previously characterized to be benign. Copy number losses or disruption by fusion will also be considered deleterious irrespective of their presence in the aforementioned databases. Gene amplifications or variants of unknown significance will not be eligible for inclusion. Patients are eligible if they have a deleterious alteration in one of these pre-specified HR genes, including: BRCA1/2, PALB2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, NBN, ARID1A and GEN1. Secondary Objectives: • Evaluate the safety and tolerability of niraparib as defined by CTCAE v5. • Determine progression free survival (PFS) with niraparib in above mentioned patient population. • Evaluate disease control rate (DCR) Exploratory Objectives: • Assess the correlation between high genome wide LOH in the tumor samples and response to treatment with niraparib. • Analyze mechanisms of resistance to PARP inhibitors. We will mainly analyze reversion mutations in HR genes as a potential mechanism of resistance.

	• Analyze EZH2 expression and its correlation with response and resistance to PARP inhibitors • Analyze germline mutations of HR genes from DNA collected from blood samples and correlation with response to niraparib. • Correlate CTCs with response to treatment.
STUDY DESIGN	Phase II: Single arm, Simon two stage design Estimated sample size: 43 patients In stage I, 18 patients will be treated, and if 2 or fewer responses are observed, the trial will be stopped early for futility. If the trial goes on to stage II, an additional 25 patients will be enrolled. If the total number responding is 7 or less by the end of stage II, the drug will not be considered worthy of further study in this patient population. Primary Endpoint: • Best overall response rate, assessed by RECIST 1.1 criteria Secondary Endpoints: • All treatment related toxicity using CTCAE v5 • Progression free survival (PFS), defined as time D1 of treatment to disease progression by RECIST 1.1 or death from any cause, whichever occurs first • Disease control rate as defined as stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) by RECIST 1.1 Brief Description: Patients can be prescreened for the study at the time of diagnosis of locally advanced or metastatic disease by determining presence of LOH high status and/or deleterious alterations in HR pathway genes in the most recent available tumor tissue or blood sample or in blood if they are found to have germline mutations. Patients with either somatic or germline mutations will be allowed. At the time of disease progression, patients with high LOH or deleterious alterations in HR pathway genes and satisfying all other inclusion criteria will be enrolled on the study. Patients will be treated with niraparib (flat dose) orally every day for 28 days until disease progression, unacceptable side effects, withdrawal of consent, or death. CT of the chest/abdomen/pelvis will be performed every 2 months and response will be assessed by RECIST 1.1.
KEY ELIGIBILITY CRITERIA (See Section 3 for complete eligibility criteria)	Inclusion Criteria: 1. Locally advanced esophageal adenocarcinoma or proximal gastric adenocarcinoma or metastatic adenocarcinoma originating from esophagus, GE junction, or proximal stomach who progress/recur beyond 2 months of receiving a platinum- containing regimen. **NOTE:** Patients can be pre-screened for study at any time including after surgical resection for locally advanced esophageal cancer, at

	presentation with metastatic disease and potentially during chemotherapy and radiation prior to surgery. 2. Patient should not have received more than 2 prior lines of chemotherapy in the metastatic setting but could have received immunotherapy, VEGF2 directed therapy, and/or trastuzumab. 3. One of the following genetic results is required for eligibility: • High LOH in tissue **OR** • HR mutation in tissue. **OR** • HR mutation in liquid biopsy **OR** • Germline mutation (blood) **NOTE:** Mutations, deletions or loss by fusions are the acceptable alterations in HR genes as long as they are deleterious. Patients are eligible if they have a mutation in pre-specified HR genes BRCA1/2, PALB2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, NBN, ARID1A and GEN1. Deleterious mutations in HR genes are defined as those that have been previously characterized to be loss-of-function/pathogenic/or likely pathogenic as specified per the following databases: Clinvar, OncoKB, or BRCAExchange. Mutations or small insertions or deletions that results in truncation, frameshift, stop codon loss, or stop codon gain will also be considered deleterious irrespective of their presence in the aforementioned databases unless previously characterized to be benign. Copy number losses or disruption by fusion will also be considered deleterious irrespective of their presence in the aforementioned databases. Gene amplifications or variants of unknown significance will not be eligible for inclusion. **NOTE:** Genetic testing results from a CLIA certified lab that confirm one of the following: high LOH in tissue, HR mutation in tissue or liquid biopsy or germline mutation in blood are required and can be used to meet eligibility. Even if a subject has met eligibility with one of the criteria above, results from the other analysis is required if available. If prior genetic results are not available, a subject must have archival tissue or fresh tissue (by new biopsy) for eligibility testing. Both primary tumor tissue and metastatic site sample biopsies are allowed. Blood will also be required for germline mutation analyses. If a subject has met eligibility with prior genetic results but does not have sufficient archival tissue for central confirmation, a biopsy is not required. 4. ECOG PS 0-1 and adequate renal, hepatic, bone marrow function as detailed in the protocol <u>Exclusion Criteria</u>: 1. Prior therapy with a PARP inhibitor 2. Disease progression during first 2 months of standard dose platinum-based chemotherapy (platinum refractory). This excludes low dose platinum based therapy that is given in a chemotherapy-radiation regimen for locally advanced esophageal cancer.

STATISTICAL CONSIDERATIONS	Null Hypothesis: ORR with niraparib in patients with metastatic esophageal/GEJ/proximal gastric adenocarcinoma previously treated with at least one line of platinum-based chemotherapy is 10% or less (based on historical response rate with single agent 2nd line chemotherapy in this disease). Alternative Hypothesis: ORR with niraparib in patients with metastatic esophageal/GEJ/proximal gastric adenocarcinoma previously treated with at least one line of platinum-based chemotherapy is 25% or greater. Acceptable Type I and type II errors: Acceptable Type I (alpha) error: up to 5% Acceptable Type II (beta) error: up to 20% (Power 80%) Estimated sample size: 43 patients using single arm, Simon two stage design In stage I, 18 patients will be treated, and if 2 or fewer responses are observed, the trial will be stopped early for futility. If the trial goes on to stage II, an additional 25 patients will be enrolled. If the total number responding is 7 or less by the end of stage II, the drug will not be considered worthy of further study in this patient population. Analytic plan for primary objective: Best overall response and ORR will be summarized descriptively. ORR is the proportion of patients with a best overall response of CR and PR (at any time up to and including the defined analysis cut-off point) and will be summarized with the point estimate and corresponding exact 95% confidence interval. An exact binomial test will be used to test the null vs alternative hypothesis Analytic plan for secondary objectives: • We will use descriptive statistics to summarize adverse events (AEs)/serious adverse events (SAEs), laboratory data, and vital signs that will be collected for all patients. • PFS will be estimated using Kaplan-Meier method and median PFS and 95% confidence interval estimated. • Disease control rate will be analyzed similarly to the primary endpoint
TOTAL NUMBER OF SUBJECTS	N = 43
ESTIMATED ENROLLMENT PERIOD	24 months

ESTIMATED STUDY DURATION	42 months

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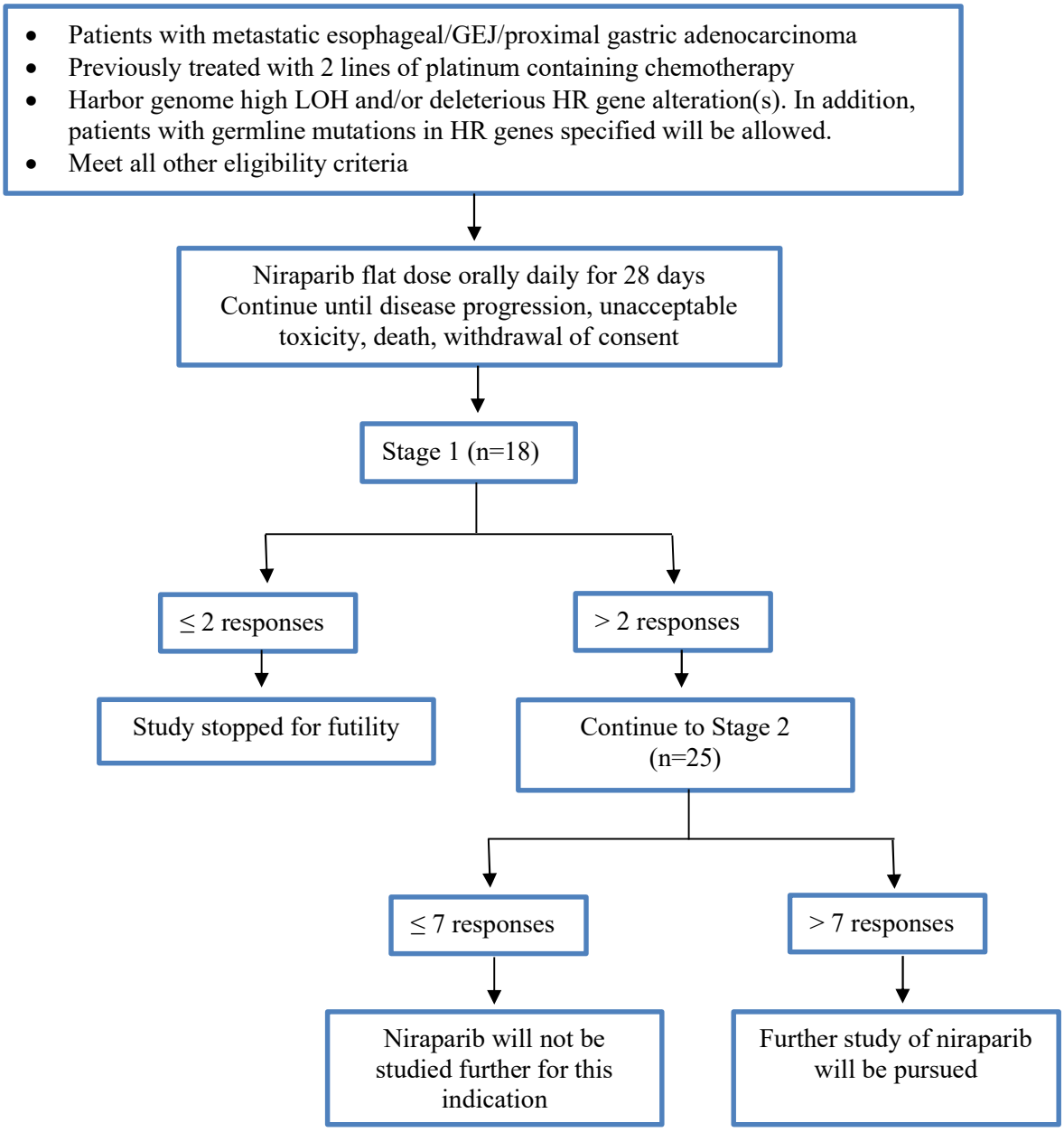
SCHEMA


Patients with metastatic esophageal/GEJ/proximal gastric adenocarcinoma
Previously treated with 2 lines of platinum containing chemotherapy
Harbor genome high LOH and/or deleterious HR gene alteration(s). In addition, patients with germline mutations in HR genes specified will be allowed.
Meet all other eligibility criteria
Niraparib flat dose orally daily for 28 days
Continue until disease progression, unacceptable toxicity, death, withdrawal of consent
Stage 1 (n=18)
≤ 2 responses
> 2 responses
Study stopped for futility
Continue to Stage 2 (n=25)
≤ 7 responses
> 7 responses
Niraparib will not be studied further for this indication
Further study of niraparib will be pursued

1. BACKGROUND AND RATIONALE

1.1 Esophageal adenocarcinoma

Esophageal cancer is the 8th most common cancer globally and the 6th most common cause of cancer death. Nearly 0.5 million patients are diagnosed with esophageal cancer annually [1]. Adenocarcinoma of the esophagus and gastroesophageal junction (GEJ) is the fastest rising cancer in the US and the Western world. Adenocarcinoma of the esophagus is the most common histology diagnosed in the US and the western world. The main risk factor for esophageal adenocarcinoma is acid reflux leading to chronic DNA damage which explains the high mutational burden noted in esophageal/GEJ adenocarcinomas [2]. Outcomes are extremely poor as the majority of patients present with either locally advanced or metastatic disease. Only a third of patients diagnosed with locally advanced esophageal cancer are cured. The majority of patients relapse and ultimately succumb to the disease. Median overall survival with currently available chemotherapy regimens is 12 months in patients with metastatic disease. Five year survival of esophageal cancer remains at 17%. There is an immense need for new therapies in this disease.

The standard of care in the first line treatment of HER2 negative metastatic esophageal adenocarcinoma is a platinum-based regimen most commonly in combination with a fluoropyrimidine[3]. FOLFOX is one of the most commonly used regimens in the first line setting of HER2 negative metastatic esophageal adenocarcinoma. Response rate is 40-50% with median progression free survival of 6 months[4]. Second line treatment options are limited and mainly include docetaxel single agent with a partial response rate of 7% and ramucirumab alone or in combination with paclitaxel[5] [6]. The combination of ramucirumab with paclitaxel has significant toxicity especially in patients with neuropathy from FOLFOX[7]. In addition not all patients qualify for ramucirumab with the risk of bleeding that exists as a result of primary esophageal tumors that at times are ulcerated. Herceptin is the only FDA approved targeted treatment based on the TOGA trial where it was shown to improve survival in combination with chemotherapy in the quarter of patients harboring HER2 amplification[8]. Targeted treatments have otherwise been lacking in esophageal adenocarcinoma.

1.2 Homologous Recombination in esophageal adenocarcinoma

Esophageal adenocarcinoma especially of the distal esophagus and gastroesophageal junction results from decades of gastroesophageal reflux induced DNA damage. During gastroesophageal reflux disease, esophageal cells are exposed to refluxate which contains gastric acid frequently mixed with duodenal bile[9]. This may lead to mucosal injury and Barrett's metaplasia (BE) the most important factors contributing to development of esophageal adenocarcinoma. Multiple forms of acid induced DNA damage have been described including DNA single strand breaks (SSBs), double strand breaks (DSBs) and reactive oxygen species (ROS). These changes are induced by the combination of low pH and bile acid [10] [11]. Severe DNA damage can lead to apoptosis but in addition can result in changes consistent with Barretts' esophagus [12] [13]. In fact, Barretts' esophagus cell lines seem more resistant to the DNA damage induced by gastroesophageal reflux disease and Barretts' esophagus potentially represents one of mechanisms for overcoming acid induced DNA damage. Homologous recombination defects have been described in esophageal adenocarcinoma and potentially occur in response to the DNA damage noted in the environment[14]. In fact, analysis of the TCGA shows abnormalities

in HR genes (figure 2) can be seen in at least 40% of patients with esophageal adenocarcinoma. Our analysis of the TCGA in figure 2 highlights the HR genes that are mutated or amplified in esophageal adenocarcinoma. Figure 3 highlights the prevalence of HR abnormalities in esophageal adenocarcinoma TCGA data.

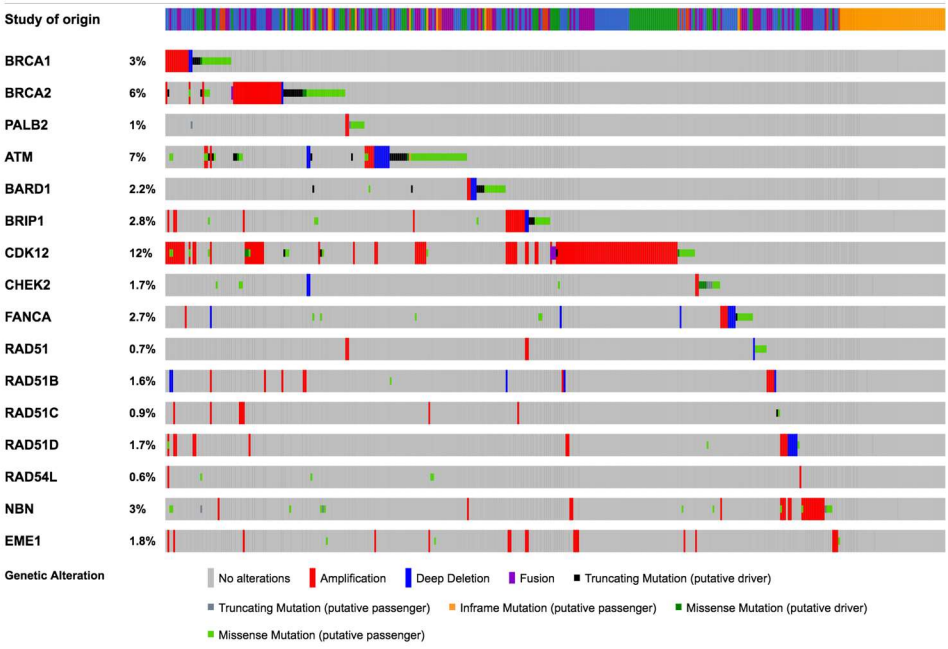


Figure 2:TCGA analysis of esophageal cancer

Published Data from our laboratory shows dysregulation of HR in esophageal adenocarcinoma with overexpression of RAD51, EME1 and BRCA1. RAD51 overexpression has been shown in esophageal adenocarcinoma and in multiple myeloma to lead to chromosomal abnormalities and genomic instability[14] [15] HR plays a major role in genome integrity maintenance through the repair of DNA DSBs. Therefore HR dysregulation is likely to lead to chromosomal rearrangements or high LOH [16]. Sensitivity to PARP inhibition has been shown to be a surrogate for HR defects or what has at times been described as BRCAness phenotype[17] [18]. Unpublished data from our laboratory support that the PARP inhibitor, BMN673 (Talazoparib), has significant single agent activity in SK-GT-4, OAC, and FLO-1 esophageal adenocarcinoma cell lines with IC50s in the 10-60 nM range. These findings in addition to published data showing high response rates of HR defective prostate cancer and ovarian cancer to PARP inhibitors and the frequency of HR abnormalities in esophageal adenocarcinoma provides the basis for the study of PARP inhibitor

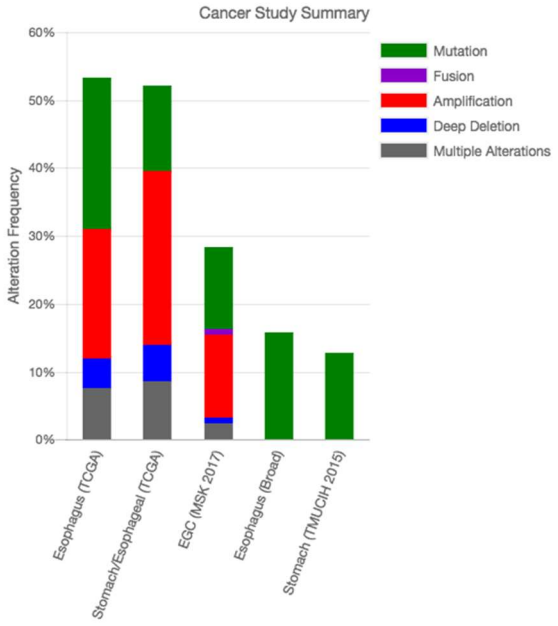


Figure 3: Prevalence of HR alterations in esophageal cancer

activity in the subset of esophageal/GEJ/proximal gastric adenocarcinomas with HR defects or high genome wide LOH[19].

Genetic alterations of different HR pathway genes are associated with human cancers, with the percentage of tumors affected by HR defects varying considerably across different tumor types [16]. An alternative approach to identifying patients with HRD due to mechanisms other than a BRCA mutation is to detect genomic scars within the tumor, which arise from the error-prone DNA repair pathways when HR is compromised. One such method is to assess genomic scarring by quantifying the extent of LOH (Loss of Heterozygosity) across the tumor genome (tumor genomic LOH). LOH has been shown to correlate with response to PARP inhibitors[20]. LOH is noted in 15-20% of patients with esophageal adenocarcinoma based on our analysis of the TCGA data. The newly recognized molecular subtypes of stomach and esophageal adenocarcinoma vary in the likelihood of harboring high LOH with the chromosomal instable tumors showing highest LOH frequency.

1.3 Background of PARP and Homologous Recombination Deficiency

Poly(ADP-ribose) polymerase (PARP)1 and PARP2 are zinc-finger deoxyribonucleic acid (DNA)-binding enzymes that play a crucial role in DNA repair[18].Upon formation of DNA breaks, PARP binds at the end of broken DNA strands, a process that activates its enzymatic activity.

Activated PARP catalyzes the addition of long polymers of adenosine diphosphate (ADP)-ribose onto PARP and several other proteins associated with chromatin, including histones and various DNA repair proteins[21] [22]. This results in chromatin relaxation, fast recruitment of DNA repair proteins, and efficient repair of DNA breaks. In this manner, PARP plays a key role in sensing DNA damage and converting it into intracellular signals that activate the base excision repair (BER) and single-strand break repair pathways. Normal cells repair up to 10,000 DNA defects daily, and single-strand breaks are the most common form of DNA damage. Cells that are unable to repair this burden of DNA damage, such as those with defects in the homologous recombination or BER pathways, are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. They enter the S phase (DNA replication) of the cell cycle with unrepaired single- and double-strand breaks. Pre-existing single-strand breaks are converted to double-strand breaks as the replication machinery passes. Accumulated double-strand breaks present during S phase are repaired by homologous recombination. Homologous recombination is the preferred repair pathway because it is associated with a much lower error rate than other forms of repair. Cells that are unable to perform DNA repair via homologous recombination (e.g., due to inactivation of genes required for homologous recombination, such as breast cancer [*BRCA1*]- or breast cancer 2 [*BRCA2*]-mutated cells) are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. These cells accumulate stalled replication forks during S phase and are more likely to use the error-prone nonhomologous end joining (NHEJ) or alternative (alt)-NHEJ pathways to repair double-strand breaks in DNA. Accumulation of errors in DNA by NHEJ contributes to mutation burden that promotes the development of cancer. Over time, the buildup of excessive DNA errors in combination with the inability to complete S phase (because of stalled replication forks) contributes to cell death[21] [22].

Treatment with PARP inhibitors could represent a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline *BRCA* mutation (g*BRCA*mut) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on NHEJ, alt-NHEJ, and BER for maintenance of genomic integrity. PARP inhibitors block alt-NHEJ and BER, forcing tumors with BRCA deficiencies to use the error-prone NHEJ to fix double-strand breaks[18]. Non-*BRCA* deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors[23]. The rationale for anticancer activity in a subset of non-g*BRCA*mut tumors is that they share distinctive DNA repair defects with g*BRCA*mut carriers, a phenomenon broadly described as "BRCAness"[24]. DNA repair defects can be caused by germline or somatic alterations to the homologous recombination DNA repair pathway. In a recent analysis of approximately 500 high-grade serous ovarian adenocarcinoma tumors, approximately 50% contained homologous recombination defects[25] A subset of these tumors had biologically plausible molecular alterations that may make them sensitive to PARP inhibition by niraparib. A similar analysis of triple-negative breast cancer indicates that 43% to 44% of these patients have tumors with homologous recombination defects[26] Homologous recombination is a complex pathway, and several genes other than BRCA1 and BRCA2 are required either to sense or repair DNA double-strand breaks via the homologous recombination pathway. Germline mutations in PALB2, BRCA1 and RAD51C have been reported in both patients with esophageal and gastric cancers[27]. Therefore, PARP inhibitors are also selectively cytotoxic for cancer cells with deficiencies in DNA repair proteins other than *BRCA1* and *BRCA2*.[18] [24] [28].

Recent clinical studies have shown PARP inhibitors to be active in breast and ovarian cancer. Clinical anticancer activity with PARP inhibitors has been seen in both patients with g*BRCA*mut and without g*BRCA*mut; however, activity is more robust in patients with the germline mutation.[18] [23] [29-35] PARP inhibitors have significant activity in prostate cancer that harbors mutations in ATM and ATR genes, in addition to BRCA1 and BRCA2 mutations[36] [37] [19]. In summary, treatment with PARP1/2 inhibitors represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair. Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of the tumor cells than that of normal cells. In fact it has been suggested that all cancers display defects in DNA repair and exploiting these defects can have significant impact on the landscape of cancer treatment [38]. PARP inhibitors have not been studied in esophageal adenocarcinoma. One study evaluated the combination of olaparib with paclitaxel in gastric cancer and did not meet its primary endpoint yet that study was not in a defined molecular subset[39]. However as previously mentioned there is strong scientific rationale for assessing the activity of PARP inhibitors in the molecularly defined subset of esophageal and gastric cancers with HR defects.

1.4 Niraparib

1.4.1 Background of Niraparib

Niraparib is a potent, orally active PARP1 and PARP2 inhibitor being developed as a treatment for patients with tumors that harbor defects in the homologous recombination DNA repair pathway or that are driven by PARP-mediated transcription factors.

1.4.2 Nonclinical Experience

Nonclinical data on niraparib are discussed in detail in the niraparib Investigator's Brochure (IB). Briefly, in nonclinical models, niraparib has been observed to inhibit normal DNA repair mechanisms and induce synthetic lethality when administered to cells with homologous recombination defects. In a *BRCA1*-mutant xenograft study, niraparib dosed orally caused tumor regression, which was mirrored by a >90% reduction in tumor weight compared with control. In a *BRCA2*-mutant xenograft study, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib displayed strong antitumor activity in *in vivo* studies with BRCA1-mutant breast cancer (MDA-MB-436), BRCA2-mutant pancreatic cancer (CAPAN-1), and with patient-derived Ewing sarcoma mice models. Utilizing patient-derived ovarian and breast cancer xenograft models, niraparib demonstrated response in both BRCAmut and BRCA wild-type tumors.

1.4.3 Clinical Experience

Niraparib clinical data are discussed in detail in the niraparib IB. In the Phase 1 clinical program, niraparib, as a monotherapy or in combination with chemotherapy, has been administered to 144 patients.

Phase 1 Study of Niraparib Monotherapy in Advanced Solid Tumors

Niraparib clinical data are discussed in detail in the niraparib IB. In the Phase 1 clinical program, niraparib, as a monotherapy or in combination with chemotherapy, has been administered to 144 patients.

Phase 1 Study of Niraparib Monotherapy in Advanced Solid Tumors

Clinical activity data for niraparib administered as monotherapy in patients with ovarian cancer are available from 1 early-phase clinical study. In Parts A and B of the Phase 1 study PN001 (ClinicalTrials.gov identifiers: MK-4827-001 and 2008_501), 100 patients with advanced solid tumors who had received a median of 3 prior therapies were enrolled; 49 patients had ovarian cancer (13 platinum-sensitive, 35 platinum-resistant, and 1 platinum-refractory)[31]

The most common nonhematological TEAEs were nausea, fatigue, anorexia, constipation, vomiting, and insomnia. These TEAEs were mainly mild to moderate in severity, self-limiting, and manageable with standard treatments. Hematological toxicity appeared to be dose proportional and most frequently arose in the setting of cumulative doses. Anemia was reported in 48 (48%) of 100 patients and was Grade ≥3 in 10 (10%) of 100 patients. Thrombocytopenia was less common (35 [35%] of 100 patients) and was Grade ≥3 in 15 (15%) of 100 patients. Neutropenia was the least commonly reported (24 [24%] of 100 patients), and was Grade 3 in

4 (4%) of 100 patients at niraparib doses of 300 and 400 mg. In all cases, hematological TEAEs were uncomplicated and reversible. Twenty patients required dose reductions (usually by 1 dose level) for recurrent anemia or thrombocytopenia. Treatment was discontinued due to AEs in 7 patients, including the 4 patients who had DLTs during the first cycle and 3 patients who had Grade 3 vomiting, Grade 2 prolongation of QT interval, and Grade 3 prolongation of QT interval. No treatment-related deaths occurred.

Of the 49 patients, 22 had confirmed BRCA1 or BRCA2 mutation, of whom 20 were radiologically assessable. Eight (40%) of these 20 patients achieved a confirmed partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) and cancer antigen 125 (CA-125) Gynecologic Cancer Intergroup criteria at doses ranging from 80 to 400 mg per day. Median response duration was 387 days (range: 159 to 518 days). Three (33%) of 9 patients with platinum-resistant BRCAmut ovarian cancer had a partial response (PR) by RECIST and CA-125 criteria. In patients with platinum-sensitive disease, 5 (50%) of 10 patients (95% CI: 19 to 81) with BRCA1 or BRCA2 mutations had RECIST and CA-125 responses.

Phase 3 Study of Niraparib Monotherapy in Platinum-sensitive, Recurrent Ovarian Cancer
In the randomized, double-blind, Phase 3 NOVA trial (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer), a total of 553 patients were randomized at 107 centers worldwide[33]. Patients were categorized according to the presence or absence of a g*BRCA*mut (g*BRCA* cohort and non-g*BRCA* cohort) within their tumors and the type of non-g*BRCA*mut and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily (QD). The primary end point was PFS. The study enrolled 203 patients in the g*BRCA*mut cohort and 350 patients in the non-g*BRCA*mut cohort. Among the 350 patients in the non-g*BRCA*mut cohort, 162 had tumors that were identified as homologous recombination deficiency positive (HRDpos), and 134 had tumors that were HRD negative (HRDneg). HRD status was not determined for 54 patients.

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

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

Table 1: Progression-Free Survival in Ovarian Cancer Patients in NOVA
Source: PR-30-5011-C (NOVA main) CSR

Abbreviation: CI = confidence interval; CSR = clinical study report; gBRCAmut = germline BRCA mutation; HR = hazard ratio; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; NE = not evaluated; PFS = progression-free survival.

[a] PFS is defined as the time in months from the date of randomization to progression or death.
[b] Based on stratified log-rank test using randomization stratification factors.
[c] Based on the stratified Cox proportional hazards model using randomization stratification factors.

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

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

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

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib. In the Phase 3 NOVA study, the incidence of MDS/AML in patients who received niraparib

(5 of 367; 1.4%) was similar to its incidence in patients who received placebo (2 of 179; 1.1%). Guidance on monitoring patients for new AEs of MDS/AML and the follow-up of patients with suspected MDS/AML is provided.

Study PR-30-5011-C1 (NOVA corrected QT interval [QTc] substudy; n = 26) is an open-label evaluation of the effects of niraparib on QTc measurements in patients with histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. There were no reports of clinically significant abnormal electrocardiogram (ECG) changes, including QTc interval prolongation, attributed to niraparib. Administration of niraparib at the therapeutic dose did not prolong the QT interval. There was no correlation between the exposure level (ie, plasma concentration) of niraparib and QTc changes (i.e., change in corrected QT interval calculated using Fridericia's formula [ΔQTcF]).

Baseline Platelet Count and Weight as Predictors of Thrombocytopenia
An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase I study, PN001. This analysis determined that only baseline platelets had an impact on platelet nadir; lower baseline platelets (<180 10^9/L) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76%) or Grade ≥ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, Grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24%) compared to patients in the highest quartile (10%).

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

Finally, a classification tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing ≥Grade 3 thrombocytopenia within 30 days after the first dose of niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg **or** baseline platelet count <150,000 µL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of patients with a body weight >77 kg **and** a platelet count >150,000 µL. Further, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000 µL, and was only 206 mg for patients with body weight < 77 kg or platelet count <150,000 µL. Thus, the actual

delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. These observations are to be confirmed in the present study with the inclusion of study treatment dosed at 200 mg (2 capsules of niraparib or placebo) in patients whose baseline weight is <77 kg or baseline platelet count is <150,000 μL.

1.5 Rationale for this study

PARP inhibitors are synthetically lethal to tumor cells with homologous recombination repair deficiency (HRD). HRD can result from deleterious *BRCA1/2* mutations or other mechanisms. HRD leads to a common phenotype of genome-wide loss of heterozygosity (LOH) and is associated with sensitivity to PARP inhibitors in ovarian cancer and other malignancies such as prostate cancer. Esophageal and stomach adenocarcinomas demonstrate a high frequency of HRD and LOH. Targeted treatments are lacking and our preclinical data shows a potential role for PARP inhibition in the treatment of esophageal cancers. HRD and LOH are potential robust biomarkers for predicting response to PARP inhibition. Other biomarkers include the clinical observation that platinum refractory tumors are less likely to respond to PARP inhibition. In this study we will exclude patients that progress during the first 2 months of platinum-based therapy for metastatic disease or within 2 months of chemotherapy and radiation for locally advanced disease. We will assess LOH and correlation with response to PARP inhibitors as a correlative endpoint.

1.5.1 Rationale for the HR genes selected

We analyzed the TCGA database and selected the HR genes with reported deleterious alterations in esophageal and stomach cancers. In addition, we reviewed the literature including prostate cancer NEJM paper and included HR genetic alterations with most likely sensitivity to PARP inhibition[19]. We included at-Rich Interaction Domain IA(ARID1A) as one of the genes to be tested. ARID1A is a tumor suppressor that is mutated in a broad spectrum of human cancers. It is recruited to DNA double strand breaks (DSBs) via its interaction with the upstream DNA damage checkpoint kinase ATR. It facilitates efficient processing of DSB to single strand ends and sustains the DNA damage signaling. Deficiency or loss of ARID1A sensitizes cancer cells to PARP inhibitors both *in vitro* and *in vivo*. Based on precision genomics clinic data at our IUSCC, ARID1A is mutated in 7% of esophageal adenocarcinoma. Based on analysis of TCGA data and a recent retrospective analysis performed by Foundation and presented at ASCO GI symposium, ARID1A is mutated in 9% of esophageal adenocarcinomas and 20% of gastric adenocarcinomas[42]. In addition we included GEN1, a holliday junction endonuclease that plays a role in repair of DNA DSBs and is mutated in 2% of esophageal adenocarcinomas[40]. The remaining genes included were selected due to their role in the homologous recombination pathway. Tumors that are BRCA mutated have been associated with extreme sensitivity to PARP inhibitors as a result of synthetic lethality. This phenomena while most known with BRCA mutations has been noted in alterations in a number of the HR genes including ATM, PALB2. Only genes with potential role in PARP inhibitor sensitivity or leading to genome instability manifested as wide loss of loss of heterozygosity were included.

1.5.2 Rationale for excluding squamous cell carcinoma of the esophagus

Esophageal adenocarcinoma and squamous cell carcinoma vary greatly in the biology, risk factors and outcomes. Esophageal squamous cell carcinomas were found to share more similarities with head and neck squamous tumors than esophageal adenocarcinomas. On the

other hand, growing evidence shows that esophageal cancer and stomach cancer share many similarities on a biological level. Our study will therefore include esophageal and stomach adenocarcinomas but not squamous cell carcinomas of the esophagus.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Determine objective response rate (ORR) with niraparib in patients with metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma previously treated with platinum containing chemotherapy and harboring high genome wide loss of heterozygosity (LOH) or defective homologous recombination noted through deleterious alterations in HR genes. Genes analyzed will include: BRCA1/2, PALB2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, NBN, ARID1A and GEN1. Patients can have somatic and/or germline mutations. Deleterious mutations in HR genes are defined as those that have been previously characterized to be loss-of-function/pathogenic/or likely pathogenic as specified per the following databases: Clinvar, OncoKB, or BRCAExchange. Mutations or small insertions or deletions that results in truncation, frameshift, stop codon loss, or stop codon gain will also be considered deleterious irrespective of their presence in the aforementioned databases unless previously characterized to be benign. Copy number losses or disruption by fusion will also be considered deleterious irrespective of their presence in the aforementioned databases. Gene amplifications or variants of unknown significance will not be eligible for inclusion. Patients are eligible if they have a deleterious alteration in one of these pre-specified HR genes, including: BRCA1/2, PALB2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, NBN, ARID1A and GEN1.

2.1.2 Secondary Objectives

- Evaluate the safety and tolerability of niraparib as defined by CTCAE v5.
- Determine progression free survival (PFS) with niraparib in above mentioned patient population.
- Evaluate disease control rate (DCR)

2.1.3 Correlative/Exploratory Objectives

- Assess the correlation between high genome wide LOH in the tumor samples and response to treatment with niraparib.
- Analyze mechanisms of resistance to PARP inhibitors. We will mainly analyze reversion mutations in HR genes as a potential mechanism of resistance.
- Analyze EZH2 expression and its correlation with response and resistance to PARP inhibitors.
- Analyze germline mutations of HR genes from DNA collected from blood samples and correlation with response to niraparib.
- Correlate CTCs with response to treatment.

2.2 Endpoints

2.2.1 Primary Endpoint

- ORR will include confirmed complete response (CR) + confirmed partial response (PR) and will be determined as per RECIST 1.1.

2.2.2 Secondary Endpoints

- Occurrence of all treatment related toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
- PFS is defined as the time from D1 of treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death as a result of any cause, whichever occurs first.
- Disease control rate is defined as the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of 0-1 within 14 days prior to registration.

4. Locally advanced esophageal adenocarcinoma or proximal gastric adenocarcinoma or metastatic adenocarcinoma originating from esophagus, GE junction, or proximal stomach who progress/recur beyond 2 months of receiving a platinum- containing regimen.

   NOTE: Patients can be pre-screened for study at any time including after surgical resection for locally advanced esophageal cancer, at presentation with metastatic disease and potentially during chemotherapy and radiation prior to surgery.

5. A subject with symptomatic brain metastasis may be considered if they have completed their treatment for brain metastasis at least 4 weeks prior to study registration, have been off of corticosteroids for ≥ 2 weeks, and are asymptomatic. Patients with asymptomatic brain mets that are untreated will be allowed.

6. Must not have received more than 2 prior lines of chemotherapy in the metastatic setting (could have received immunotherapy, VEGF directed therapy, and/or trastuzumab which does not count as chemotherapy).

7. One of the following genetic results is required for eligibility:
   - High LOH in tissue **OR**
   - HR mutation in tissue **OR**
   - HR mutation in liquid biopsy **OR**
   - Germline mutation (blood)

   NOTE: Mutations, deletions or loss by fusions are the acceptable alterations in HR genes as long as they are deleterious. Patients are eligible if they have a mutation in pre-specified HR genes BRCA1/2, PALB2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, NBN, ARID1A and GEN1. Deleterious mutations in HR genes are defined as those that have been previously characterized to be loss-of-function/pathogenic/or likely pathogenic as specified per the following databases: Clinvar, OncoKB, or BRCAExchange. Mutations or small insertions or deletions that results in truncation, frameshift, stop codon loss, or stop codon gain will also be considered deleterious irrespective of their presence in the aforementioned databases unless previously characterized to be benign. Copy number losses or disruption by fusion will also be considered deleterious irrespective of their presence in the aforementioned databases. Gene amplifications or variants of unknown significance will not be eligible for inclusion.

   NOTE: Genetic testing results from a CLIA certified lab that confirm one of the following: high LOH in tissue, HR mutation in tissue or liquid biopsy or germline mutation in blood are required and can be used to meet eligibility. Even if subject has met eligibility with one of the criteria above, results from the other analysis is required if available.

   If prior genetic results are not available, subject must have archival tissue or fresh tissue (by new biopsy) for testing. Both primary tumor tissue and metastatic site sample biopsies are allowed. Blood will also be required for germline mutation analyses. Central confirmation of all results will be performed but is not mandated for eligibility. If a subject has met eligibility with prior genetic results but does not have sufficient archival tissue for central confirmation, a biopsy is not required. Prior results from liquid biopsy can be used for eligibility. This may not be confirmed centrally.

8. Presence of measurable disease by RECIST v1.1, defined as:
   - Tumor lesions that must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
     - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
     - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
     - 20 mm by chest X-ray
   - Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed.

9. Prior cancer treatment must be completed at least 14 days prior to registration and the subject must have recovered from all reversible acute toxic effects of the regimen (other than alopecia) to ≤ Grade 1 or baseline.

10. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 14 days prior to registration.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1.5 K/mm^3
Hemoglobin (Hgb)	≥ 9 g/dL
Platelet Count (Plt)	≥ 100 K/ mm^3
Renal	
Creatinine	≤ 1.5 X upper limit of normal (ULN)
Hepatic	
Bilirubin	≤ 1.5× ULN ((≤2.0 in patients with known Gilberts syndrome))
Aspartate aminotransferase (AST)	≤ 2.5× ULN*
Alanine aminotransferase (ALT)	≤ 2.5 × ULN*

* unless liver metastases are present in which case AST/ALT must be ≤ 5x ULN

11. Females of childbearing potential must have a negative pregnancy test within 7 days prior to study treatment. Urine or serum βhCG if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

12. Females of childbearing potential must be willing to abstain from heterosexual intercourse or use adequate contraception as described in Section 5.4. Males must be willing to abstain from heterosexual intercourse or use adequate contraception as described in Section 5.4.

13. Participants must agree to not breastfeed during the study or for 30 days after the last dose of study treatment.

14. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.

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

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Prior therapy with a PARP inhibitor.

2. Disease progression during first 2 months of standard dose platinum-based chemotherapy (platinum refractory). This excludes low dose platinum based therapy that is given in a chemotherapy-radiation regimen for locally advanced esophageal cancer.

3. Participant must not be simultaneously enrolled in any other interventional clinical trial.

4. Participant must not have had major surgery ≤ 3 weeks prior to initiating protocol therapy and participant must have recovered from any surgical effects.

5. Participant must not have received investigational therapy ≤ 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is shorter, prior initiating protocol therapy.

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

7. Participant must not have a known hypersensitivity to niraparib components or excipients including tartrazine.

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

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

10. 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.

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

12. Participant must not have 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.

13. No active secondary cancer.

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy **within 7 business days** of registration.

5. TREATMENT PLAN

5.1 Pre-Medication and Hydration

There is no required premedication or hydration.

5.2 Niraparib Administration

Niraparib will be administered as a flat-fixed daily dose according to the Table 2 below. A cycle will equal 28 days. Participants should take their dose at approximately the same time each day. Bedtime administration may be a potential method for managing nausea. Niraparib should be swallowed whole and not opened, crushed or chewed. Food does not significantly affect the absorption of niraparib; therefore, niraparib may be taken without regard to meals. Vomited doses should not be made up. If a participant misses a dose (greater than 12 hours from normal dosing time) of niraparib, they should skip that dose and take their next dose at its regularly scheduled time. Niraparib will be dispensed as a one-month supply. Subjects will be asked to complete a pill diary and bring the diary with the pill bottle to each clinic visit.

If niraparib is dose reduced, participants should be instructed to continue using their current supply at their new dose until their supply has been exhausted. Participants must be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed and documented.

Patients will receive niraparib until disease progression or unacceptable toxicities.

Table 2: Niraparib Dosing

Baseline Criteria	**Starting Dose**
≥ 77 kg **and** ≥ 150,000 µL platelets	300 mg (3 x 100 mg capsules)
< 77 kg **or** < 150,000 µL platelets	200 mg (2 x 100 mg capsules)

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

5.3 Concomitant Medications

5.3.1 Allowed Concomitant Medications

All treatments the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

5.3.2 Prohibited Concomitant Medications

The following medications are prohibited while receiving protocol therapy:

- Systemic anticancer (chemotherapy) or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than niraparib.
- Radiation therapy encompassing >20% of the bone marrow is prohibited within 2 weeks prior to Day 1 and during study treatment. **NOTE:** Palliative radiation therapy to a small field >1 week prior to Day 1 of study treatment may be allowed. This should be discussed with the sponsor-investigator and communicated to the project manager at HCRN Any surgery that involves tumor lesions. **NOTE:** Administration of radiation therapy or surgery done that involves tumor lesions will be considered as disease progression at the time the procedure is performed.
- 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.
- Prophylactic cytokines (i.e., granulocyte colony-stimulating factor [GCSF]) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current American Society of Clinical Oncology (ASCO) guidelines.[25]

5.4 Contraception

Women of childbearing potential who are sexually active must agree to abstain from heterosexual intercourse or use adequate contraception beginning with time of consent, during the study treatment and for 180 days after last dose of study treatment(s). Males must be willing to abstain from heterosexual intercourse or use a condom from the time of informed consent until 90 days after treatment discontinuation. This timeframe also applies to sperm donation. If not contraindicated, use of a barrier and hormonal method is suggested. See below for options:

Acceptable non-hormonal birth control methods:

- Total sexual abstinence: refrain from any form of sexual intercourse in line with the patients' usual and/or preferred lifestyle. Abstinence must be for the total duration as described above. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion
- Intrauterine Device. Provided coils are copper-banded.
- Male condom

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon®, Norplant®)
- Normal and low dose combined oral pills
- Hormonal shot or injection (eg, Depo-Provera)
- Intrauterine system device (eg, levonorgestrel-releasing intrauterine system - Mirena®)

5.5 Breast Feeding
Participants must not breast-feed while receiving protocol therapy and for 30 days following the last dose of protocol therapy.

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

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS
The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Niraparib
- Dose interruption and/or modification of niraparib may be implemented due to nonhematologic or hematologic toxicities per the site investigator's judgement after Cycle 1.
- Treatment must be interrupted for any nonhematologic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 AE that the site investigator considers to be related to administration of niraparib (Table 3). Dose adjustments are not required for AEs or abnormal laboratory values assessed by the treating physician as not clinically significant. If the nonhematologic toxicity is appropriately resolved to baseline or Grade ≤ 1 within 4 weeks (28 days) of the dose interruption period, the patient may restart treatment with niraparib but with a dose level reduction if prophylaxis is not considered feasible (see Table 5). If the event recurs at similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made according to Table 3.
- If the toxicity requiring dose interruption has not resolved completely or to Grade 1 during the maximum 4-week (28-day) dose interruption period, and/or the patient has already undergone a dose reduction to a minimum dose of 100 mg QD, the patient must permanently discontinue treatment with niraparib.
- The dose interruption and modification criteria for niraparib for hematologic parameters will be based on blood counts and are outlined in Table 5. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period, the patient must permanently discontinue treatment with niraparib.
- For patients whose initial dose is 3 capsules daily (300 mg/day), dose reductions to 2 capsules daily (200 mg/day) and subsequently to 1 capsule daily (100 mg/day) will be allowed. No further dose reduction will be allowed.
- For patients whose initial dose is 2 capsules (200 mg/day), dose reduction to 1 capsule once daily (100 mg/day) will be allowed. No further dose reduction will be allowed.

Table 3: Recommended Dose Modifications for Adverse Reactions

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

Table 4: Niraparib Dose Modifications for Nonhematologic Adverse Reactions

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

NOTE: Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Pre-existing hypertension should be adequately controlled before starting niraparib treatment. Blood pressure and heart rate should be monitored at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with niraparib.

In the clinical program, blood pressure measurements were obtained on Day 1 of each 28 day cycle while the patient remained on niraparib. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without niraparib dose adjustment. Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of niraparib dose, if necessary. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension (per investigator discretion) cannot be adequately controlled with antihypertensive therapy.

There have been rare reports (0.09% of clinical trial patients) of niraparib-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES). PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib.

Table 5: Niraparib Dose Modifications for Hematologic Toxicity

Laboratory Abnormality	Intervention
Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If dose interruption and/or modification is required at any point during study treatment because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until the AE resolves to the specified blood count levels. To ensure the safety of the new dose, weekly blood draws for CBC will be required for an additional 4 weeks after the AE has resolved, after which monitoring every 4 weeks may resume. CBC monitoring will continue every 4 weeks (ie, monthly) for the next 11 months of treatment, and periodically after this time. Any patient requiring transfusion of platelets or red blood cells (≥1 unit) must undergo a dose reduction upon recovery if study treatment is resumed.	
Platelet count < 100,000/μL	First occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at same or reduced dose per Table 3. If platelet count is < 75,000/μL, resume niraparib at a reduced dose per Table 3.
	Second occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at a reduced dose per Table 3. Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil count < 1,000/μL	Withhold niraparib for a maximum of 28 days and monitor blood counts until neutrophil counts return to ≥1,500/μL. Resume niraparib at a reduced dose per Table 3. Discontinue niraparib if neutrophil level has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone maximum dose reductions per Table 3.
Hemoglobin ≤ 8 g/dL	Withhold niraparib for a maximum of 28 days and monitor blood counts until hemoglobin returns to ≥ 9 g/dL. Resume niraparib at a reduced dose per Table 3. Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone maximum dose reductions per Table 3.

Hematologic adverse reaction requiring transfusion	For patients with platelet count ≤ 10,000/μL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Resume niraparib at a reduced dose per Table 3.
Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.

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

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

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

6.2 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF)

- Documented disease progression by RECIST 1.1
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy (“refuses treatment”), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Serious or life-threatening adverse event
- Severe noncompliance with protocol as judged by the site investigator or sponsor-investigator
- Participant is diagnosed with MDS or AML (as confirmed by a hematologist)
- Investigator, sponsor-investigator, and/or GSK becomes aware of conditions or events that suggest a possible risk or hazard to participants if the clinical study continues

6.3 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject’s protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 28 days	Screening	Cycle 1		Cycle 2 +	Safety follow up visit[12]	Long-term Follow up[13]
	-28 days	Day 1	Day 15 ± 3 days	Day 1 ± 3 days	30 days (+7) post last dose	(±14 days)
REQUIRED ASSESSMENTS						
Informed Consent	X					
Medical History[1]	X					
Physical Exam	X	X		X	X	
Vital signs and ECOG Performance Status[2]	X	X[2]	X	X[2]	X	
Review AEs, con meds, pill diary[3]	X	X		X	X	
LABORATORY ASSESSMENTS						
Complete Blood Cell Count with diff (CBC)	X	X[11]	X[11]	X[11]	X	
Comprehensive Metabolic Profile (CMP)	X	X[11]		X[11]	X	
Pregnancy test (serum or urine) (WOCBP)[4]	X	X		X[4]	X	
DISEASE ASSESSMENT						
CT of chest[5]	X			X[5]		
CT or MRI of abdomen and pelvis[5]	X			X[5]		
TREATMENT EXPOSURE						
Niraparib		X	X	X		
SPECIMEN COLLECTION						
Archival Tissue or Fresh Tissue by Biopsy[6]	X[6]					
Standard of Care Biopsy[6]					X[6]	X[6]
Whole Blood for CTCs[7]		X		X[7]	X[7]	X[7]
Plasma for ctDNA[8]		X			X[8]	X[8]
Whole Blood for eligibility[9]	X[9]					
BANKING SAMPLES						
Whole blood[10]		X[10]				
FOLLOW-UP						
Survival Status, Subsequent Therapy						X

CBC with differential and platelet to include: WBC, ANC, Hgb, Hct, PLT and lymphocyte count. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

Key to Footnotes

1: Medical History; other data to obtained during this assessment includes: diagnosis and staging to include pathology report and staging documentation. Smoking history questionnaire and trial awareness question. In addition, prior anti-cancer treatment should be documented including medications (chemotherapy, checkpoint inhibitors, etc) radiation or surgery. **NOTE**: Genetic testing results from a CLIA certified lab that confirm one of the following: high LOH in tissue, HR mutation in tissue or liquid biopsy or germline mutation in blood are required and can be used to meet eligibility. Even if subject has met eligibility with one of the criteria above, results from the other analysis are required if available.

2: Vital signs to include blood pressure, temperature, heart rate, weight, and height (screening only) and ECOG performance status. Blood pressure and heart rate will be required weekly for the first 2 months of study treatment (C1D1, C1D8, C1D15, C1D21, C2D1, C2D8, C2D15, C2D21), monthly for first year, and periodically thereafter. This may be performed at a clinic visit or with an at home device. Subjects will be asked to document the results and bring to each clinic visit.

3: AE assessment and concomitant medication review should include confirmation of study medication taken within the last visit. Subjects will be asked to complete a pill diary and bring the diary to each visit with the pill bottle. In addition, assessment for AML/MDS should be performed (review of CBC and patient symptoms). For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to GSK. A copy of the hematologist's report of aspirate/biopsy findings including a classification according to WHO criteria and other sample testing results related to MDS/AML will be provided to the sponsor-investigator and to GSK.

4: For women of childbearing potential (WOCBP): urine or serum βhCG if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Testing is required for screening then 7 days prior to initiation of study treatment. During treatment, pregnancy test should be done every 3 cycles for WOCBP and at safety follow up visit.

5: Tumor response assessment will consist of evaluation by CT scans of chest and MRI or CT of abdomen and pelvis at screening and every 2 cycles starting after screening with Cycle 3 (imaging selected for each subject should remain the same throughout the study); tumor imaging to be done at treatment discontinuation is at discretion of site investigator. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated. Window of ± 7 days for post screening scans.

6: **REQUIRED:** If prior genetic results are not available, subject must have archival tissue or fresh tissue (by new biopsy) for eligibility testing. Both primary tumor tissue and metastatic site sample biopsies are allowed. In patients without known genetic alterations that qualify them for trial, archival tissue must be identified during screening or pre-screening and if not available, subjects must undergo a biopsy for fresh tissue at screening for eligibility purposes and correlative analysis. If a subject has met eligibility with prior genetic results but does not have sufficient archival tissue for central confirmation, a biopsy is not required. If patient has been previously tested and known to harbor an alteration that makes them eligible, archival tissue (if available) will be submitted for centralized testing however it is not mandatory. Refer to the Correlative

Laboratory Manual (CLM) for additional details. **OPTIONAL**: If a standard of care biopsy is done at progression, a sample for correlative analysis will be requested. Consent from the subject will be obtained for this sample. This progression biopsy sample will include both, FFPE and flash frozen sections. Refer to CLM for additional details.

7: REQUIRED: Whole blood for analysis of circulating tumor cells (CTCs) will be drawn prior to treatment C1D1, Day 1 of every odd cycle beginning with Cycle 3 and at the time of disease progression. Subjects that discontinue study treatment for a reason other than progression should have these samples drawn at progression. Subjects that discontinue study treatment due to progression may have these samples drawn at the safety follow up visit. Refer to CLM for additional details.

8: REQUIRED: Plasma for ctDNA will be drawn prior to treatment C1D1 and at the time of disease progression. Subjects that discontinue study treatment for a reason other than progression should have these samples drawn at progression. Subjects that discontinue study treatment due to progression may have these samples drawn at the safety follow up visit.

9: REQUIRED: Whole Blood for analysis of germline mutations of HR genes will be drawn during screening. Sample may be used for liquid biopsy if tumor tissue is insufficient for testing. Refer to CLM for additional details.

10: OPTIONAL: Blood for banking: Whole blood will be collected prior to treatment on Cycle 1 Day 1. Refer to CLM for additional details.

11: If screening (baseline) labs were performed within 7 days of Cycle1 Day 1 of treatment, these do not need to be repeated. Follow up labs and clinic visits may be done up to 72 hours prior to the time points designated above. CBCs should be collected weekly for the first Cycle. If dose interruption and/or modification is required at any point during study treatment because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until the AE resolves to the specified blood count levels. To ensure the safety of the new dose, weekly blood draws for CBC will be required for an additional 4 weeks after the AE has resolved, after which monitoring every 4 weeks may resume. CBC monitoring will continue every 4 weeks (ie, monthly) for the next 11 months of treatment, and periodically after this time.

12: The safety follow-up visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (+7 days) after the last dose of treatment. Subjects who have an ongoing Grade ≥ 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

13: Subjects who discontinue study treatment without radiographically documented PD will continue to be evaluated per institutional standards until time of disease progression, death or until study completion, except when not feasible in the opinion of the site investigator due to subject's clinical status. After the subject has documented PD, radiologic assessments are no longer required and the subject will be followed every 3 months (± 14 days) until the subject's death or study completion, whichever is earlier. Follow up will be 5 years from the D30 safety follow up visit. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

8. BIOSPECIMEN STUDIES AND PROCEDURES

Please refer to the CLM for additional details regarding biospecimen studies and procedures.

8.1 Tissue

8.1.1 Archival Tissue or Fresh Tissue prior to Treatment

If prior genetic results are not available, subject must have archival tissue or fresh tissue (by new biopsy) for eligibility testing. Both primary tumor tissue and metastatic site sample biopsies are allowed. In patients without known genetic alterations that qualify them for trial, archival tissue must be identified during screening or pre-screening and if not available, subjects must undergo a biopsy for fresh tissue to determine if they are eligible. If patient has been previously tested and known to harbor an alteration that makes them eligible, archival tissue (if available) will be submitted for centralized testing however it is not mandatory.

EZH2 expression will be performed on pre-treatment tumor tissue when available. Increased EZH2 expression has been postulated as a mechanism of resistance to PARP inhibitors. Tissue for HR mutation analysis (BRCA1/2, PALB2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, NBN, ARID1A) will be collected. Additional tissue collected will be analyzed for EZH2 baseline expression and possibly LOH.

EZH2 expression by IHC will be performed on initial tumor sample and on optional standard of care biopsies collected at time of disease progression. EZH2 is enhancer of zeste homolog 2. EZH2 is an enzymatic subunit of PRC2 complex which is essential in multiple gene silencing. EZH2 is frequently overexpressed or mutated in cancers and is overexpression in esophageal cancer. EZH2 is oncogenic and has been recently implicated in resistance to PARP inhibitors. PARP inhibition has been shown to increase EZH2 activity and diminish response to PARP inhibition. We will therefore assess baseline EZH2 expression in tumor samples prior to initiation of therapy and at time of disease progression{Yamaguchi, 2018 #207}.

8.1.2 Standard of Care Biopsy at Progression

If a standard of care biopsy is performed at progression, a sample will be requested for correlative analysis. Consent will be obtained from subjects for this sample. This sample will be used to look at reversion mutations of HR genes as mechanisms of resistance and EZH2 analyses. This biopsy sample will include both, FFPE and flash frozen sections.

8.2 Peripheral Blood Samples

8.2.1 Required Whole Blood for Circulating Tumor Cells (CTCs)

Whole Blood is required for analysis of CTCs prior to C1D1, Day 1 of every other Cycle beginning with Cycle 3 and at the time of disease progression or safety visit.

8.2.2 Required Blood Sample for Plasma for ctDNA

Blood samples for plasma will be drawn prior to treatment C1D1 and at the time of disease progression/safety follow up visit.

8.2.3 Required Whole Blood Sample for Germline Mutations and ctDNA

Whole Blood sample for analysis of germline mutations of HR genes from DNA and correlation with response to niraparib and eligibility for trial. This sample may also be used for liquid biopsy panel if archival tissue sample is insufficient for testing. This sample is required and should be collected at screening.

8.3 Banking Samples for Future Unspecified Cancer Related Research

Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.

8.4 Storage of Biospecimens

Any specimens remaining (leftover) once protocol described biospecimen-based studies are complete will be stored for future unspecified cancer related research. Permission for storage of samples will be obtained from subjects during informed consent.

8.5 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's sequence ID assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

The following sections describe the recommended method to track disease response for solid tumor trials as per the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 (see Eisenhauer EA et al. *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Can, 2009.45:p.228-247). Refer to the RECIST 1.1 publication for complete details on these criteria.

9.1 Measurable Disease

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

9.1.1 Malignant Lymph Nodes

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

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.3 Target Lesions

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

9.4 Non-target Lesions

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

9.5 Evaluation of Target Lesions

NOTE: Also see the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
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.			

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.8 Definitions for Response Evaluation – RECIST 1.1

9.8.1 First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

9.8.2 Confirmation of Response
To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

9.8.3 Objective Response Rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.4 Disease Control Rate
The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.5 Progression Free Survival
A measurement from the date of D1 of treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

10 DRUG INFORMATION
Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

10.1 Niraparib
Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl}phenyl]piperidine[tosylate monohydrate salt]) is an orally available, potent, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) -1 and -2 inhibitor. Niraparib is also known as ZEJULA.

10.1.1 Storage and Stability
Niraparib is supplied by GSK in high-density polyethylene (HDPE) bottles with child-resistant plastic closures. The study treatment will be open-label and will not be participant-specific.

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

10.1.2 Handling and Disposal
Niraparib should be destroyed at the investigational site if permitted by local regulations.

10.1.3 Dispensing and Accountability

GSK will supply niraparib at no charge to subjects participating in this clinical trial.

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 storage and handling manual.

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

All dispensing and accountability records should be stored in accordance to the institution regulations. The pharmacist will dispense study treatment for each participant according to the protocol and storage and handling manual, if applicable.

10.1.4 Adverse Events

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

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

11 ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v5 will be utilized for AE assessment. A copy of the CTCAE v5 can be downloaded from the CTEP website at http://ctep.cancer.gov

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

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.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death.
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Adverse Events of Special Interest (AESI)

Selected non-serious AEs and SAEs are also known as Adverse Events of Special Interest. Any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the site investigator to the sponsor-investigator and GSK is required.

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

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

AESI should be collected and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the sponsor-investigator and GSK for any patient who has received niraparib (regardless of the timeframe since the last dose).
- Embryo-fetal toxicity should be reported as outlined in the Pregnancy reporting section.

11.1.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Per regulatory requirements, if an event is assessed by the sponsor-investigator as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the sponsor-investigator to submit the SUSAR Regulatory Authorities according to applicable regulations. In addition, the SUSAR will be distributed to the Investigators/sites, utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and GSK per the governing institutional requirements and in compliance with local laws and guidelines. HCRN will facilitate reporting of SUSARs between sites to sponsor-investigator and GSK.

11.1.5 Pregnancy

Site investigators must report all pregnancies and the outcomes to the sponsor-investigator and to GSK. The sponsor-investigator has the responsibility to monitor the outcome of all pregnancies reported during the clinical study. Each pregnancy must be reported by the site investigator to HCRN on an Initial Pregnancy Report Form **within 24 hours** of becoming aware of the pregnancy. HCRN will then report to GSK **within 24 hours** of becoming aware of the pregnancy. Pregnancy is not an AE, and therefore does not need to be reported as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. The site investigator must follow-up all pregnancies, document the course and the outcome, and report this information to HCRN **within 24 hours** of becoming aware who will report to GSK on a Pregnancy Outcome Report Form **within 24 hours** of becoming aware - even if the patient was withdrawn from the study or the study has finished. An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy on the Pregnancy Outcome Report Form. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

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

11.1.6 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.7 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs considered by the site investigator to be related to study medication and unexpected are reported regardless of the timeframe from last dose of study medication.
- All at least possibly related and unexpected SAEs will be reported on the SAE Submission Form within **24 hours of becoming aware of the initial event or follow-up information**.
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.
- Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented but not reported as an SAE. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.

The site will submit the completed SAE Submission Form to HCRN **within 24 hours of becoming aware of the initial event or follow-up information.** The form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed above), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs to GSK

HCRN will report SAEs that are at least possibly related and unexpected to GSK **within 24 hours** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to GSK as it is received from site.

Email: OAX37649@gsk.com
Fax: +44(0) 208754 7822

11.2.3 Quarterly AE/SAE Reporting to GSK

On a quarterly basis HCRN will provide GSK with a line listing of all adverse events (serious and non-serious) received during a defined quarter. The line listing will include a sequence

number, the AE term, onset date, outcome, causality assessment, and study drug dosing information.

11.2.4 Reporting Product 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 site to HCRN and HCRN will report to GSK via email: gsk-rd.complaints@gsk.com **within 1 working day** of first becoming aware of the possible defect. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

11.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.4 HCRN Responsibilities to FDA

For protocols exempt from the requirements of an IND, HCRN will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11.5 IND Safety Reports Unrelated to this Trial

GSK will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system. Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL METHODS

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima, and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol; however all changes from the original analysis plan will be documented in the final study report. The statistical analysis methods are outline below.

12.1 Study Design

This is a single arm two-stage Phase II Study Evaluating safety and efficacy of niraparib in patients with previously treated homologous recombination (HR) defective or loss of heterozygosity (LOH) high metastatic esophageal/gastroesophageal junction/proximal gastric adenocarcinoma.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

- Overall Response rate (ORR) is defined as CR plus PR by RECIST 1.1.

12.2.2 Definition of Secondary Endpoints

- Toxicities will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
- PFS is defined as the time from D1 of treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death as a result of any cause whichever comes earlier.
- Disease Control rate (DCR) per RECIST is defined as stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1 from the start of treatment to disease progression/recurrence.

12.3 Sample Size and Accrual

This is a standard Simon two-stage design. The null hypothesis is that the ORR is 10% and the alternative hypothesis is that the ORR is 25%. The Type I (alpha) error is 5% and power is 80%. The power stated is for testing the alternative vs null hypothesis at Stage 2 given the two-stage design. In stage I, 18 patients will be treated, and if 2 or fewer responses are observed, the trial will be stopped early for futility. After patient 18 is accrued, enrollment will be halted for this analysis. The analysis at Stage 1 is for futility, and there is no decision made to reject the null hypothesis at Stage 1. If the trial goes on to stage II, an additional 25 patients will be enrolled. If the total number responding is 7 or less by the end of stage II, the drug will not be considered worthy of further study in this patient population. Accrual is expected to be 1-2 patients per month. There will be no replacements for patients that are not evaluable for ORR or are not compliant with therapy. They will be treated as non-responders if they are not evaluable for ORR.

12.4 Analysis Datasets

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Evaluable	This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation.
Safety	This will comprise all subjects that have received one dose of study drug.

12.5 Data Analysis Plans

12.5.1 Analysis Plans for Primary Objective

For the Phase II study, the primary endpoint of objective response rate (per RECIST) in the evaluable population will be summarized with the point estimate and corresponding exact 95% confidence interval. An exact binomial test will be used to test the null vs alternative hypothesis.

12.5.2 Analysis Plans for Secondary Objectives

Toxicity will be described for the safety population with frequency tables. Progression free survival will be estimated in the evaluable population using standard Kaplan-Meier curve. The median PFS will be estimated along with the corresponding 95% confidence interval. DCR will be analyzed similarly to the primary endpoint.

12.5.3 Analysis Plans for Exploratory Objectives

LOH, mRNA expression and alterations/mutations of HR genes in tumor sample, and HR gene expression/alterations in circulating tumor cell derived xenografts will be described with means, median, standard deviation, minimum and maximum. The correlation of ORR and DCR with correlative variables will be analyzed using a two-sample t-test or Wilcoxon rank sum test. Cox regression will be used for PFS.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the Indiana University Melvin and Bren Simon Cancer Center's (IUSCC) DSMP for Moderate Risk Trials.

HCRN facilitated oversight activities for Moderate Risk Trials include:

- Review and processing of all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator.

- Investigators will conduct continuous review of data and patient safety. For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure), the sponsor investigator will notify HCRN who will notify the DSMC Chair and Compliance Officer immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/package insert.
- Notify participating sites of adverse events potentially requiring expedited reporting and subsequent DSMC recommendations for study modifications.
- Coordinate *monthly* meetings which will include representation from each accruing site.
    - These meetings should include review of data, the number of subjects and significant toxicities as described in the protocol. HCRN should maintain meeting minutes and attendance for submission to the DSMC upon request.
- Conduct data monitoring across all participating sites in accordance with the monitoring requirements set forth in the IUSCC DSMP.

13.2 IUSCC Data Safety Monitoring Committee Oversight

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study to assess toxicity, compliance, data integrity, and accrual per the Institutional DSMP. Trials managed by HCRN are not routinely audited or monitored by IUSCC; however, the IUSCC DSMC retains the right to audit HCRN trials on a for cause basis.

The IUSCC DSMC will review study data annually during the active treatment and safety follow-up portion of the trial, per the IUSCC DSMP.

In preparation for the IUSCC DSMC review, HCRN will provide the following:

- Monthly Summary Reports
- Reports of the following, if not already included in the Monthly Summary Report:
    - Adverse event summary report (including serious adverse events)
    - Study accrual patterns
    - Protocol deviations
- Audit and/or monitoring results, if applicable
- Data related to stopping/ dose decision rules described in study design
- HCRN monthly study meeting minutes/ attendance

Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. The IUSCC DSMC will notify the sponsor-investigator and other regulatory bodies, as appropriate, for issues of immediate concern. The sponsor-investigator will work with HCRN to address the DSMC's concerns as appropriate.

At any time during the conduct of the trial, if it is the opinion of the sponsor-investigator that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the DSMC Chair and Compliance Officer. Alternatively, the DSMC may initiate suspension or early closure of the study at any time based on its review of the study reports.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and will be transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

Participating sites may also be subject to quality assurance audits by GSK or its designee as well as inspection by appropriate regulatory agencies.

13.3.1 Onsite Monitoring

Monitoring visits to the trial sites will be made periodically during the trial, to ensure key aspects of the protocol are followed. For cause visits may occur as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by GSK or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform (EDC system), a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source

document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, GSK, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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