A Phase 1 Evaluation of the Safety and Tolerability of Niraparib in Combination with Everolimus in Advanced Gynecologic Malignancies and Breast Cancer

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

Confidentiality Statement

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SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Phase 1 Evaluation of the Safety and Tolerability of Niraparib in Combination with Everolimus in Advanced Gynecologic Malignancies and Breast Cancer

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

_____ _____

Casey Williams, PharmD **Date**

Chief Scientific Officer

INVESTIGATOR SIGNATURE PAGE

Declaration of the Investigator

Title: A Phase 1 Evaluation of the Safety and Tolerability of Niraparib in Combination with Everolimus in Advanced Gynecologic Malignancies and Breast Cancer

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

Investigator

_____ _____

Casey Williams, PharmD **Date**
Chief Scientific Officer

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LIST OF ABBREVIATIONS AND DEFINITIONS

Table 1 List of Abbreviations

Abbreviation	Definition
ADP	adenosine diphosphate
AE	adverse event
AUC	area under the curve
BER	base excision repair
BRCA	breast cancer gene
CBC	complete blood count
CL	oral clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
FE	food effect
gBRCA	germline breast cancer gene
GCSF	granulocyte-colony stimulating factor
GBM	glioblastoma multiforme
hCG	human chorionic gonadotropin
HR	homologous recombination
HRD	homologous recombination deficiency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NHEJ	non-homologous end joining
PARP	poly(ADP-ribose) polymerase
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PRO	patient reported outcomes
PS	performance status
QD	once a day
SAE	serious adverse event
TEAE	treatment emergent adverse event
TMZ	temozolomide
ULN	upper limit normal

1 INTRODUCTION

1.1 General Background

The treatment of patients with advanced cancer remains unsatisfactory. New combinations are needed to improve the outcomes for patients with advanced disease. Thus, successful treatment of ovarian and breast cancer represents a great challenge. The optimal combination, sequencing of treatment, and schedule for targeted drugs and chemotherapy has not been optimally established. Little is also known regarding the unique molecular characteristics and patterns of each individual's cancer tumor cells. New pathway-driven molecular subtypes are just now being elucidated[1] and clinical trials with molecularly targeted therapy, for example, in the different types of ovarian and breast tumors are urgently needed using theranostic information[2,3].

Therapies are being developed to primarily reduce signaling via oncogenic intracellular pathways and thereby change transcriptional events that take place within the cancer cell nucleus. These novel therapies may potentially benefit not only ovarian and breast cancer patients but all tumor types and at all stages in the cancer process. Previously, factors used to make traditional chemotherapy decisions were based on the tissue of origin or histological subtype. But now, in the era of precision medicine, therapeutic strategies must be based on the degree of addiction of an individual tumor to the pathway being targeted. Identifying the oncogenic drivers of solid tumors and having drugs that target these drivers and/or pathways are the keys to the successful treatment of cancer in the future.

1.2 Ovarian Cancer

As an example of solid tumors in women, ovarian cancer is the seventh most common cancer in women (and the 18th most common cancer overall) worldwide. Approximately 239,000 cases were recorded in 2012, accounting for nearly 4 percent of all new cases of cancer in women (2 percent overall). This cancer is usually fatal, and is the eighth most common cause of cancer death in women worldwide (14th overall)[4]. Cancers of the ovary, fallopian tube, and peritoneal origin exhibit similar behaviors and clinical and molecular characteristics. As such, these are often combined together and define epithelial ovarian cancer (EOC). About 85– 90% of ovarian cancers are epithelial carcinomas.

Patients with ovarian cancer often have no symptoms at the early stages, so the disease is generally advanced when it is diagnosed. Approximately 75 percent of women have stage III (disease that has spread throughout the peritoneal cavity or that involves lymph nodes) or stage IV (disease spread to more distant sites) disease at diagnosis. The 5-year survival rate ranges from approximately 30–50%[5,6]. Risk increases with age, although the rate of increase slows after the menopause. Only 10–15% of cases occur before menopause.

Classically, EOC is treated with primary debulking surgery (PDS) followed by adjuvant platinum and taxane-based chemotherapy. However, for poor surgical

candidates and patients in whom an optimal cytoreduction (residual disease <10 mm) is not feasible, neoadjuvant chemotherapy (NACT) prior to interval surgery and adjuvant chemotherapy is an alternative option. The search for novel therapeutic combinations and strategies that will drive precision medicine are paramount if we are to make a dent in increasing survival rates.

1.3 Breast Cancer

In the United States, approximately 180,000 new cases of breast cancer occur annually, and there are more than 40,000 deaths[7]. More than 150,000 cases develop each year in Canada and the European community together, resulting in over 60,000 deaths from breast cancer[7]. The vast majority of patients who die from breast cancer succumb to metastatic disease.

Breast cancer is currently viewed as a complex family of diseases with individual molecular features and corresponding behaviors[8]. Early research in breast cancer identified the role of estrogen and estrogen receptors in tumor stimulation and growth. This discovery led to the development and approval in 1977, of the very first molecularly targeted cancer therapy, tamoxifen, for the treatment of metastatic breast cancer[9,10]. Significant advances have also been made in identifying genetic risk factors, e.g. BRCA-1 and BRCA-2, and other preventive strategies. Gene assays of breast tumor cells have been developed to estimate and predict the risk ratio of disease recurrence with and without adjuvant therapy[11,12].

Endocrine therapy and chemotherapy (using either sequential single agents or combination regimens) remain the principal treatments for women with metastatic breast cancer. The success of endocrine therapy is dependent on tight regulation of breast cell growth by steroids and growth factor receptors[13]. However, as cancer progresses, it usually becomes resistant to antiestrogens, and most patients eventually stop responding to endocrine therapy. In addition, a significant number of women have hormone receptor negative metastatic breast cancer that is not amenable to targeted therapies based on overexpression of ER, PR and/or HER2 receptor families. A wide variety of classes of chemotherapeutic agents have activity as single agents. While the use of polychemotherapy (combination) regimens is usually associated with higher response rates when compared with single-agent treatment[14], it is not clear that the enhanced response rates obtainable with currently available combination regimens correlate with clinically meaningful improvements in survival. Median survival remains approximately two years for women with metastatic breast cancer, and less than 3% of patients will experience long-term survival after treatment[15].

Thus, many women continue to die from breast cancer, primarily due to complications related to metastatic disease. Despite numerous new and old chemotherapeutic, biologic and hormonal therapies available to treat metastatic breast cancer, it remains the second leading cause of death in American women with 39,520 deaths estimated for 2011, second only to lung cancer[16]. Clearly a new approach in treating advanced breast cancer is needed and therefore, the

development of new treatment strategies is essential to improving outcomes for patients with advanced breast cancer.

1.4 Background of PARP and PARP Inhibition

The PARP family consists of 17 members of which PARPs- 1, -2, -5A, and -5B, uniquely catalyze the transfer of multiple ADP-ribose units[17,18]. PARP1 and 2 are zinc-finger DNA binding enzymes that play a crucial role in DNA repair. Upon formation of DNA breaks, PARP binds at the end of broken DNA strands, a process that activates its enzymatic activity. Activated PARP catalyzes addition of long polymers of ADP-ribose onto PARP and several other proteins associated with chromatin, including histones and various DNA repair proteins. 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 (DNA replication) phase 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[19]. Homologous recombination is the preferred repair pathway because it is associated with a much lower error rate than other forms of repair. Cells unable to perform DNA repair via homologous recombination (e.g., due to inactivation of genes required for homologous recombination, such as breast cancer gene 1 [BRCA1] or BRCA2) are at risk for accumulating multiple lesions that will ultimately trigger apoptosis[20]. 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 mutations that promote 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.

1.5 Background on Homologous Recombination Deficiency (HRD)

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 ($gBRCA^{mut}$) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on nonhomologous end-joining (NHEJ), alternative (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. Non-BRCA deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors. The rationale for

anticancer activity in a subset of non-gBRCA^{mut} tumors is that they share distinctive DNA repair defects with gBRCA^{mut} carriers, a phenomenon broadly described as "BRCAness."[21] 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[22]. A subset of these tumors had biologically plausible molecular alterations that may make them sensitive to PARP inhibition by niraparib. This concept of inducing death by use of PARP inhibitors to block one DNA repair pathway in tumors with pre-existing deficiencies in a complementary DNA repair pathways is called synthetic lethality[23], the two insults together induce cell death when neither alone would have this effect.

1.6 Background of Niraparib

Niraparib is an orally active PARP1/2 inhibitor with nanomolar potency[24] being developed as a monotherapy agent for tumors with defects in the homologous recombination DNA repair pathway or that are driven by PARP-mediated transcription factors. Proof of principle was also obtained using preclinical *in vivo* xenograft BRCA mutant tumor models reviewed in Jones et al[24].

1.6.1 Phase 1 Clinical Studies

Five Phase 1 clinical studies (PN001, PN005, PN008, PN011, and PN014) were conducted in 144 patients. Patients enrolled in these studies who were tolerating treatment without significant safety issues or evidence of disease progression could continue to receive study therapy provided the Investigator felt that such treatment was in the best interest of the patient. Such actions would not preclude the possibility of future studies with niraparib as single-agent therapy or in combination with other investigative agents.

1.6.2 Phase 3 Study (PR-30-5011-C)

The main study of PR-30-5011-C is a double-blind, 2:1 randomized, placebo-controlled study in platinum-sensitive ovarian cancer patients who have either gBRCAmut or a tumor with high-grade serous histology. The patients must have received at least 2 platinum-based regimens, had a response to their last regimen, and have no measurable disease >2cm and normal CA-125 (or >90% decrease) following their last treatment. The study will assess whether maintenance with niraparib will extend progression-free survival (PFS) in this population. There are 2 independent patient cohorts in this study, one cohort of patients with deleterious gBRCA mutations (gBRCAmut) and the other composed of patients with high-grade serous histology but without such gBRCA mutations (non-gBRCAmut) based on the hypothesis that patients with gBRCA mutations will be enriched for responsiveness to niraparib. Study treatment is dispensed to patients on Day 1 and every cycle (28 days) thereafter until the patient discontinues study treatment. Study treatment is administered orally QD continuously. Three capsules of 100-mg strength are taken at each dose administration. Clinic visits occur in each cycle (every 4 weeks ± 3 days). Response Evaluation Criteria in Solid Tumors tumor assessment via

computed tomography (CT) or magnetic resonance imaging (MRI) scan of abdomen/pelvis and clinically indicated areas is required at the end of every 2 cycles (8 weeks with a window of ± 7 days from date of visit) through Cycle 14, then at the end of every 3 cycles (12 weeks with a window of ± 7 days from date of visit) until progression.

PR-30-5011-C also contains a 14-day, open-label, 2-treatment, crossover sub-study to evaluate the effect of a high fat meal on niraparib (single dose) exposure. For this food effect (FE) sub-study, entry criteria were broadened to include patients with ovarian cancer regardless of platinum sensitivity and burden of disease as long as no standard therapy exists or the patient refused standard therapy. In Group A, patients fasted (nothing to eat or drink except water) for at least 10 hours before receiving a single dose of 300 mg niraparib; patients continued to fast for at least 2 hours following the dose. In Group B, patients fasted for at least 10 hours before consuming a high fat meal. Within 5 minutes of finishing the meal, a single dose of 300 mg niraparib was administered orally and patients resumed fasting for at least 4 hours. After a 7-day PK assessment and wash-out period, all patients received their second single dose of niraparib on Day 8 under the opposite (fasting vs high fat meal) circumstance. After the completion of the 14-day food effect sub-study, patients began daily dosing at 300 mg QD niraparib on Cycle 1/Day 1.

1.6.3 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 (<180,000 μL) 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.

1.7 PARP and mTOR inhibitors

Studies are investigating ways to extend the use of PARP inhibitors in breast and other cancers despite previous inadequate and/or inconclusive data[20,25]. Various genes and signaling pathways have been implicated including the phosphoinositide 3-kinase (PI3K) pathway that contributes to repair of DSBs in addition to its role in pro-proliferative and antiapoptotic functions in tumor cells[26]. Several studies have shown that the PI3K pathway that involves PI3K-related kinases including mammalian target of rapamycin (mTOR) are involved in DSB repair and the DNA-damage response (DDR)[27,28]. Furthermore, tumor cells became sensitized to cisplatin-mediated DNA damage–induced apoptosis when RAD001 (everolimus), an mTOR inhibitor, was added to cells[27]. Patients with sporadic triple negative breast cancer (TNBC) and/or basal-like breast tumors may have a certain degree of “BRCAness” that would open up the possibility of treating them with PARP inhibitors in combination with other drugs, potentially inhibitors of the PI3K-mTOR pathway[29,30]. Use of an mTOR inhibitor such as everolimus in combination with niraparib, could 1) sensitize tumor cells to niraparib through blockade of PI3K- dependent DDR, and 2) inhibit tumor growth mediated by PI3K-mTOR survival/proliferative signals. We have recently shown that PI3K-mTOR inhibition can sensitize BRCA1-competent TNBC to PARP inhibition in both *in vitro* and *in vivo* model systems, suggesting cooperation between the DDR and PI3K pathways[29].

The combination of a PARP inhibitor with everolimus has promise in the treatment of sporadic TNBC that displays “BRCAness” characteristics. In a similar manner, other solid tumors including ovarian, in which “BRCAness” is also found could benefit from the combination of niraparib and everolimus. Thus, the use of this combination in a phase I cancer clinical trial merits further investigation.

1.8 Rationale for Current Study

PARP is a very promising target for the treatment of many malignancies. As a nick-sensor, PARP binds to and initiates the repair of DNA SSBs. A failure to repair these events leads to persistent SSBs, which otherwise would get converted into potentially clastogenic or lethal DSBs at the “replication fork.”

Correction of DSBs occurs through either homologous recombination (HR) or nonhomologous end joining (NHEJ). Thus, PARP inhibitors (PARPi) have potential chemosensitizing, radiosensitizing, and antineoplastic activities.

The phosphoinositide 3-kinase (PI3K) enzyme contributes to repair of DSBs in addition to its role in pro-proliferative and antiapoptotic functions in tumor cells. Recently, the PI3K enzyme has been demonstrated to play a critical role in RAD51 recruitment[31]. The PI3K signaling pathway has been reported to maintain HR steady state and stabilize and preserve DSB repair by interacting with the HR complex[26]. Suppression of PI3K function has been shown to impair HR[32]. mTOR, as a family member of PI3K-related protein kinases including ATM, ATR and DNA-PK, was also reported to be involved in DDR[27,28]. The kinase activity of mTOR has been particularly known to integrate nutrient/energy signaling with that of growth factor signaling in highly dividing tumor cells[33-35].

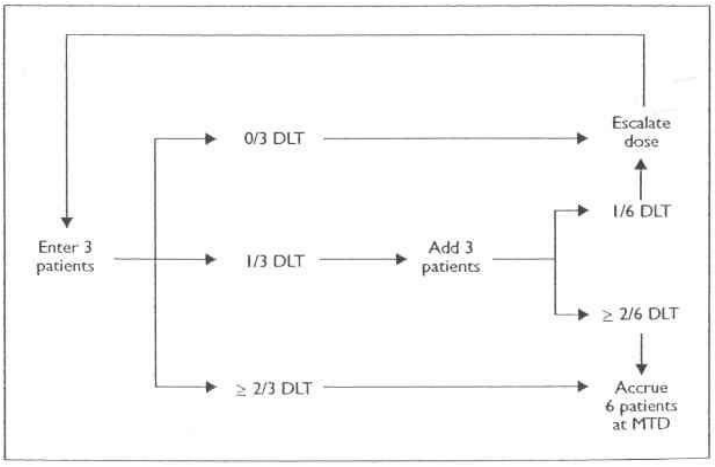
In our laboratory, we have shown through multiple preclinical experiments that the combination of a PI3K inhibitor or an mTOR inhibitor with a PARP inhibitor is synergistic in multiple cancer cell lines and *ex vivo* models. We propose to combine everolimus and niraparib in a phase I trial to determine the safety profile of this combination in advanced gynecologic malignancies and breast tumors.

2 OVERALL DESIGN AND PLAN OF THE STUDY

2.1 Overview

Open-label, cohort study to determine the feasibility and tolerability of the combination of daily niraparib and daily or thrice weekly everolimus for one 28-day cycle in patients with advanced gynecologic malignancies and breast cancer.

Figure 1: Study Design. Dosing schema, 3–6 patients per cohort.



The goal of this study is to determine a maximum tolerated dose (MTD) of the combination of niraparib and everolimus. To do this, we will estimate the MTD that is defined as the dose level at which less than one-third of patients will experience a dose-limiting toxicity (DLT). A traditional dose escalation design will be used, beginning with the lowest dose level and escalating to the maximum allowable dose level as specified in the protocol. A maximum of 4 dosing levels results in a maximum sample size of *n*=24 subjects. Adverse events will be defined using the Common Toxicity Criteria v.4.03.

One of the following outcomes will determine the treatment of subsequent patients:

- If none of the three patients experiences a DLT, the next group of patients will be entered in the next higher dose cohort. All patients within a cohort must have completed at least one cycle (28 days) prior to initiation of the next cohort of patients.
- If one of the three patients experiences a DLT, three more patients will be accrued at the current dose level. Subsequently, if only one of the six patients treated at this level experiences a DLT, the dose will be escalated to the next higher dose in the next group of patients. If two or more of the six patients experiences a DLT, the MTD has been exceeded and is defined as the previous dose at which no more than 1/3 experienced a DLT.
- If at least two of the three experience a DLT, the MTD has been exceeded and is defined as the previous dose at which no more than 1/3 experienced a DLT.

If the lowest allowable dose level exceeds the MTD, the study will be terminated and

the combination will not be deemed safe for use in this population. Additionally, the highest dose level will not be exceeded, even if no DLTs are experienced at that dose.

Once the MTD has been exceeded and this is not the lowest allowable dose, the investigators may drop down to the previous cohort and enroll an additional 6 patients to further confirm the safety and tolerability of the MTD.

We will summarize the adverse events overall and by individual AE categories. Serious adverse events will be summarized in a similar manner. These summaries will be performed overall and for each dose cohort. We will summarize all events as well as the highest grade for a given subject. We will summarize the number of subjects that exhibit a DLT at each dose cohort and describe the DLT for each subject, if applicable.

Cohort 1: (each cycle is 28 days long)
Everolimus 5mg daily on Mondays, Wednesdays, and Fridays
Niraparib 100mg daily

Cohorts 2-4 are closed to future enrollment as of April 2020.

Cohort 2: (each cycle is 28 days long)
Everolimus 5 mg daily on Mondays, Wednesdays, and Fridays
Niraparib 200 mg daily

Cohort 3: (each cycle is 28 days long)
Everolimus 2.5 mg daily
Niraparib 200 mg daily

Cohort 4: (each cycle is 28 days long)
Everolimus 5 mg daily
Niraparib 200 mg daily

2.2 Primary Objective

- To determine the maximum tolerated dose of the combination of niraparib and everolimus for the treatment of patients with advanced gynecologic malignancies or breast cancer

2.3 Secondary Objectives

- To assess the toxicity of the combination of niraparib and everolimus in each cohort
- To determine the response rate (according to RECIST 1.1 response criteria)

2.4 Exploratory Objectives

- To assess whether patients with certain molecular aberrations, using FoundationOne and/or cell-free DNA (cfDNA) or circulating tumor cells (CTCs) responded more favorably to the combination.
- To describe symptom occurrence and severity and Health Related Quality of Life (HRQOL) as measured by the TRSC and HRQOL-LASA respectively.

2.5 Inclusion Criteria

a. Patients must have a gynecologic malignancy or breast cancer (triple negative or hormone receptor positive only) that is refractory/intolerant to all therapies known to confer clinical benefit in the advanced or metastatic setting or if the patient's clinical team and the PI believe that the study treatment gives the patient the best chance for clinical benefit

b. Patients with breast cancer must have measurable disease per RECIST 1.1. criteria. Patients with ovarian cancer are eligible with or without measurable disease

c. Patients with ovarian cancer must have had appropriate surgical management for their disease and should be platinum resistant (recurrence within 6 months of last platinum-containing regimen) or be refractory to platinum-containing regimens

d. Patients with endometrial, cervical, or any other advanced gynecologic malignancy must have already received or not be a candidate for all therapy proven to have a survival benefit

e. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2

f. Patients must be ≥18 years of age

g. Patients must have adequate organ function, defined as follows:

   - Absolute neutrophil count ≥1,500/μL
   - Platelets ≥125,000/μL
   - Hemoglobin ≥10 g/dL
   - Serum creatinine ≤1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation
   - Total bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤1 x ULN
   - Aspartate aminotransferase and alanine aminotransferase ≤2.5 x ULN unless liver metastases are present, in which case they must be ≤5 x ULN

h. Patient agrees to blood draws during screening and at the end of treatment for molecular and cytogenetic analysis

i. Female patients of childbearing potential must have a negative serum pregnancy test (beta hCG) at Screening

j. Female patients of childbearing potential must agree to use an acceptable

method of birth control (excluding hormonal birth control methods, see Section 3.0.5) for 72 hours prior to initiation of therapy and to continue its use during the study and for at least 30 days after the final dose or as directed by the Investigator Brochure.

k. Male patients must agree to use an acceptable form of birth control (see Section 3.0.5) from study Day 1 through at least 90 days after the final dose or as directed by the Investigator Brochure.

l. Patients must be able to understand the study procedures and agree to participate in the study by providing written informed consent

2.6 Exclusion Criteria

a. Patients with HER2+ breast cancer measured by standard IHC or FISH testing

b. Patients must not be simultaneously enrolled in any other interventional clinical trial

c. Patients must not have had major surgery ≤3 weeks of starting the study and patient must have recovered from any effects of any major surgery

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

e. Patients must not have had radiotherapy encompassing >20% of the bone marrow

f. Patients must not have received prior treatment with a known PARP inhibitor or have participated in a study where any treatment arm included administration of a known PARP inhibitor

g. Patients must not have a known hypersensitivity to the components of niraparib, everolimus, rapamycin analogues, or the excipients

h. Patients must not be immunocompromised (patients with splenectomy are allowed)

i. Patients must not have had any known, persistent >Grade 2 toxicity from prior cancer therapy

j. Patients must not have had any known, persistent (>4 weeks), ≥Grade 3 hematological toxicity or fatigue from prior cancer therapy

k. Patients must not have received a transfusion (platelets or red blood cells) ≤4 weeks of the first dose of study treatment

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

m. Patients must not have had diagnosis, detection, or treatment of another type of cancer ≤2 years prior to randomization (except basal or squamous cell carcinoma of the skin that has been definitively treated)

n. Patients must not have known, symptomatic brain or leptomeningeal metastases

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

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

q. Patient is a woman with a positive serum pregnancy test ≤3 days prior to study drug administration, is breast-feeding, or is planning to conceive children within the projected duration of the study treatment

r. Patients with uncontrolled or poorly controlled hypertension. Patients with grade 3 hypertension or above at baseline are not allowed unless controlled (grade 1 or better) for at least three months.

s. Patients taking ACE inhibitors (patients that have no known medical reason to require therapy with ACE inhibitors may be switched to another appropriate antihypertensive treatment prior to initiation of study treatment)

t. Patients taking strong or moderate CYP3A4/PgP inhibitors or strong CYP3A4/PgP inducers (appendix 2) (if medically appropriate, patients may be switched to another appropriate therapy at least 14 days prior to initiation of study treatment)

2.7 Patient Withdrawal and Replacement

2.7.1 Discontinuation from Treatment

Patients may be discontinued from study treatment at any time. Specific reasons for discontinuing treatment include the following:

a. Serious or life-threatening adverse event

b. Risk to patients as judged by the Investigator and/or Sponsor

c. Severe noncompliance with protocol as judged by the Investigator and/or Sponsor

d. Request of the patient

e. Patient becomes pregnant

f. Progressive disease

g. Investigator becomes aware of conditions or events that suggest a possible hazard to patients if the clinical study continues

h. Patient is diagnosed with MDS or AML (as confirmed by a hematologist)

i. Patient is diagnosed with PRES

2.7.2 Discontinuation from Study

The investigator/treating physician will make every reasonable effort to keep each patient on study. However, if the investigator/treating physician removes a patient from the study or if the patient declines further participation, a final assessment of the patient's disease status should be performed prior to any therapeutic intervention. These results, together with a description of the reason for study discontinuation, must be recorded in the CRF.

Patients who discontinue from treatment will continue to receive follow-up assessments as part of the study unless they are discontinued from study by one of the following events:

- Withdrawal of consent or HIPAA Authorization
- Loss to follow-up
- Death from any cause
- Termination of the study

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

3 STUDY CONDUCT

3.1 Study Restrictions

3.1.1 Granulocyte Colony-Stimulating Factor (GCSF)

Prophylactic cytokine (Granulocyte Colony-Stimulating Factor [GCSF]) administration should not be given in the first cycle of the study, but may be administered in subsequent cycles according to local guidelines and Section 4.1.4.

3.1.2 Substrates of P-glycoprotein or Cytochrome P450

Niraparib has shown limited interactions with other drugs (see Appendix 2). The niraparib safety profile includes risk for thrombocytopenia; therefore, patients should be advised to use caution with anticoagulation and antiplatelet drugs.

Co-administration of everolimus with strong inhibitors or inducers of CYP3A4 or PgP should be avoided; they may cause changes in everolimus concentrations. For a current complete listing of cytochrome P450 metabolized medications please access the following website: www.Medicine.iupui.edu/clinpharm/ddis/table.asp. If this website is not operative, please search using Flockart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table.

Examples of agents that may increase everolimus blood concentrations: Everolimus blood concentrations may be increased by substances that inhibit CYP3A4 activity and thus decrease everolimus metabolism. Everolimus blood concentrations may be increased by inhibitors of PgP that may decrease the efflux of everolimus from intestinal cells. Concurrent treatment with strong inhibitors of CYP3A4 or PgP (including but not limited to ketoconazole, itraconazole, ritonavir, clarithromycin and telythromycin) should be avoided. Use caution when administered in combination with moderate CYP3A4 inhibitors or PgP inhibitors. If everolimus must be co-administered with a moderate CYP3A4 or PgP inhibitor, the patient should be carefully monitored for undesirable effects and the dose reduced if necessary. Concomitant treatment with moderate inhibitors of CYP3A4 including but not limited to erythromycin, verapamil, fluconazole, diltiazem, amprenavir, fosamprenavir, or aprepitant) and PgP inhibitors requires caution. Other moderate inhibitors of CYP3A4 and PgP that may increase everolimus blood concentrations include certain antifungal agents (e.g. fluconazole) and calcium channel blockers (e.g. diltiazem). Grapefruit, grapefruit juice and other foods that are known to affect cytochrome P450 and PgP activity should be avoided during treatment.

Agents that may decrease everolimus blood concentrations: Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells. Concurrent treatment with strong inducers of CYP3A4 or PgP should be avoided. If everolimus must be co-administered with a strong CYP3A4 or PgP inducer (e.g. rifampicin and rifabutin), it may be necessary to adjust the dose. Other strong inducers of CYP3A4 that may increase the metabolism of everolimus and decrease everolimus blood levels include St. John's wort (Hypericum perforatum), corticosteroids (e.g. dexamethasone,

prednisone, prednisolone), anticonvulsants (e.g. carbamazepine, phenobarbital, phenytoin,) and anti-HIV agents (e.g. efavirenz, nevirapine).

3.1.3 Other Anticancer Therapy

No other anticancer therapy is permitted during the course of the study treatment for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to enrollment, per exclusion criteria above). If the patient discontinues study treatment, this restriction no longer applies, however the patient will remain enrolled in the study for the purpose of collecting subsequent outcomes. Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment) is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.

3.1.4 Vaccines

An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown and therefore they should not be administered to patients in the study. All patients will be instructed to not receive a vaccination with a live virus vaccine until at least 30 days after the completion of the treatment, starting at the time of consent.

3.1.5 Contraception

3.1.5.1 Guidelines for Contraception

All male and female subjects who are not surgically sterile or post-menopausal are required to use ***two*** forms of birth control with the use of a condom (male or female condom; with or without spermicide) required as one of the forms of birth control.

Acceptable methods of contraception in addition to the use of a condom (male and female; with or without spermicide) include:

Female study subjects: non-hormonal intrauterine device (IUD) or diaphragm with spermicide

Female partner of study subjects: non-hormonal IUD, diaphragm with spermicide, or hormonal birth control (e.g., pills, IUD [hormonal or non-hormonal], NuvaRing)

3.1.5.2 Exemptions to Contraception

Patients must be postmenopausal, free from menses for >1 year, surgically sterilized, willing to use adequate contraception to prevent pregnancy, or agree to abstain from activities that could result in pregnancy from enrollment through3 0 days after the last dose of study treatment

3.1.6 Blood Donation

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

3.1.7 Optimal Antiemetic and Antidiarrheal Prophylaxis or Treatment

Patients should avoid use of corticosteroids and NK-1 antagonists as antiemetic prophylaxis or treatment due to drug interactions. Antiemetic prophylaxis is not recommended at the initiation of study treatment. If antiemetic therapy is required, it is recommended that ondansetron 8mg po q8 prn be the treatment of choice. Additional interventions should be discussed with the principle investigator.

Antidiarrheal therapy is also not recommended at the initiation of study treatment. If therapy is required, it is recommended that loperamide 4mg followed by 2mg every 4 hours or after each unformed stool be the standard treatment.

3.2 Study Schedule of Procedures

An overview of the study is provided in the study schedule and is shown in the Schedule of Events in Section 7.

3.3 Procedures by Visit

3.3.1 Screening Procedures/Enrollment (Visit 1, Day -28 to Day -1)

All subjects must have signed and dated the informed consent and HIPAA Authorization prior to any study specific screening procedures being performed. Pre-enrollment screening test and evaluations will be used to determine the eligibility of the patient for study inclusion. All screening tests and procedures must be completed within 28 days prior to study registration and include the following:

1) Demography and Medical History including documentation of prior regimen
2) Vital signs including: temperature, BP, pulse, respiration rate, oxygen saturation
3) Concomitant medications
4) Performance Status–-ECOG
5) CBC with differential and platelet count
6) Biochemistries including: ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, creatinine clearance (calculated using the Cockcroft formula) or creatinine and albumin
7) Lipid panel
8) Serum pregnancy test, required only for women of childbearing potential
9) Tumor Assessment according to RECIST 1.1 (only if measurable lesions; patients will not be excluded if there are no measurable lesions if they have ovarian cancer)

10) Whole blood samples will be collected prior to the start of the study drug for cytogenetic analysis if required. Samples are to be collected in K2 EDTA tubes and labeled with the protocol number, patient ID, collection date, and visit type (screening, end of treatment, or other). All samples should be stored at -20C until ready for shipment if required.

Once all screening procedures have been completed and laboratory values have been reported, the investigator/treating physician or their designee will register the patient in the study.

3.3.2 On Study

The active component of the study will be the first three cycles. The MTD will be assessed in the first cycle while cycles two and three will determine ongoing tolerability. After the completion of two cycles, patients will be assessed for disease response. Patients that have stable disease or disease response will be allowed to continue their treatment as long as there are no unacceptable toxicities and as long as their disease is stable or improving.

For the purposes of this study the following evaluations will be performed during active therapy:

1) Physical exam (including vital signs)
2) ECOG performance status
3) Concomitant medications
4) Labs including CBC with differential and Comprehensive Metabolic Panel. **CBC should be performed and monitored weekly from D14 until the end of the first cycle (D28) and then monthly thereafter**
5) Blood pressure monitoring should continue weekly for 2 cycles (8 weeks) through Cycle 3 Day 1, and if under adequate control per institutional protocols, monitoring may subsequently resume as described in Table 5
6) Adverse Event Monitoring
7) Completion of questionnaires – TRSC and HRQOL-LASA
8) In the event that a patient is diagnosed with MDS/AML while on study, a bone marrow aspirate and biopsy will be completed, and a whole blood sample will be collected for molecular and cytogenetic analysis.
9) After the completion of 2 cycles (56 days +/- 7 days) patients will be assessed for disease response utilizing the same analysis that was used at baseline and then again at 16 weeks (112 days +/- 7 days) if the patient has stable disease or better. If the patient continues on trial, scans may be performed every 8-12 weeks thereafter at the discretion of the investigators.

3.3.3 End of Treatment (within 7 days of last dose)

1) Lipid Panel
2) Whole blood sample for cytogenetic analysis

3) Adverse Event Monitoring
4) Completion of questionnaires – TRSC and HRQOL-LASA

3.3.4 Ongoing Assessments

1) Disease status assessment to be performed every 8-12 weeks (i.e. every 56-94 days +/- 7 days) at the discretion of the investigators
2) Adverse events will be monitored for 30 days following the last dose
3) Survival status will be monitored every 8 weeks for at least 2 years following the last dose
4) In the event that a patient develops MDS/AML, the patient will be followed for at least 5 years following the last dose.

3.3.5 Unscheduled Assessments

1) SAE monitoring:

- If at any time after the study is completed, an Investigator becomes aware of an SAE that is considered related to the investigational product, the Investigator should report the SAE to the Sponsor's Pharmacovigilance Department within 24 hours of becoming aware of the SAE

2) CBC:

- If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC also will be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume

3) Chest CT or MRI:

- If the chest CT or MRI is clear at Screening, repeat chest imaging is not required in the absence of lesions to be followed or in the absence of clinical indication requiring follow-up; otherwise, repeat chest imaging should be completed at the same time as RECIST imaging

4) Bone marrow aspirate and biopsy:

- For any suspected MDS/AML case reported while a patient is receiving treatment or followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the study site receives a copy of the hematologist's report, which must include a classification according to World Health Organization criteria[36]. The site must keep a copy of the report with the patient's study file.

5) Exploratory:

- To assess whether certain molecular aberrations responded more

favorably to the combination, tissue from a new or existing biopsy may be sent to Foundation Medicine for analysis. Additionally, sequencing DNA from the patients' blood samples using cell-free DNA (cfDNA) or circulating tumor cells (CTCs) technology may be used as part of the analysis. In both cases, this will be carried out in a retrospective manner and patients will not be selected based on their molecular aberrations for this study.

6) FoundationOne Assay

- Foundation Medicine has developed its first clinical product, an NGS genomic assay that is used to identify alterations in all genes known to be somatically altered in human solid tumors based on recent scientific and clinical literature. The assay generates an informative genomic profile through interrogation of the entire coding sequence of 315 cancer-related genes plus select introns from 28 genes often rearranged or altered in solid tumors. The information obtained from this assay complements traditional cancer treatment decision tools and can often expand treatment options by matching each patient with targeted therapies and clinical trials that are relevant to the molecular changes in their tumor based on the most recent scientific and medical research. DNA from the patient is sequenced at great depth to hone in on the relevant, actionable somatic alterations, including single base pair changes, insertions, deletions, copy number alterations, and selected fusions.

7) Cell Free DNA (cfDNA) and Circulating Tumor Cells (CTCs)

- Plasma of cancer patients contains cell-free tumor nucleic acid that carries information on tumor mutations and tumor burden. A range of markers has been identified for specific tumor types. Nucleic acids are found in small amounts in healthy and diseased human plasma/serum. Higher levels of circulating nucleic acids are present in the plasma of cancer patients derived from tumor cells.

4 STUDY MEDICATION

4.1 Other Agent Used in Combination: Everolimus

Everolimus will not be supplied as part of this study.

Everolimus is an antineoplastic agent. The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,35R)-1,18-dihydroxy-12-

{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.9]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone (everolimus package insert).

4.1.1 Administration

Everolimus 2.5 mg or 5 mg tablets will be used. Everolimus will be self-administered orally on a daily basis and doses will either be 5 mg (1 tablet) thrice weekly, 2.5 mg daily, or 5 mg daily depending on the cohort the patient is enrolled to. Patients may take the everolimus at the same time as the niraparib. Each cycle will be 28 days; everolimus will be taken continuously with no rest between cycles.

4.1.2 Dose Modification

No dose reductions of everolimus are allowed in cohort 1.

4.1.3 Toxicity Management

Adverse effects related to the use of everolimus should be managed based upon the information in the FDA approved package insert, published literature, and clinical discretion. It is suggested that all patients receive a steroid mouth rinse for the management of stomatitis.

4.1.4 Packaging, Labeling and Storage

Everolimus will be packaged and labeled according to pharmacy and local regulations.

4.1.5 Disposal and Destruction

Everolimus will be destroyed at the investigational site, if permitted, according to local regulations.

4.2 Niraparib

4.2.1 Identity

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP-1 and -2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate.

4.2.2 Administration

Niraparib 100 mg will be administered orally QD continuously. Niraparib will be administered as a flat-fixed dose and not by body weight or body surface area. Each dose should be swallowed whole without chewing. The consumption of water is permissible. Patients should take doses at approximately the same times each day, and record this information in the patient diary. Patients will be provided with a diary in which to record their intake of study drug. However, the actual number of tablets taken by the patient must be calculated from the number of tablets dispensed and returned.

Patients 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.

Patients may take the niraparib and the everolimus at the same time.

4.2.3 Potential Risks of Niraparib

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

The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 367 patients receiving niraparib: neutropenia, palpitations, asthenia, 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. The following adverse reactionhas been identified in less than 0.1% of patients on clinical trials receiving niraparib: posterior reversible encephalopathy syndrome (PRES). 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. Guidance on monitoring patients for new events of MDS/AML and the follow-up of patients with suspected MDS/AML is provided in in Section 4.1.4 and Section 7.

4.2.4 Dose Modification

Dose interruption may be implemented at any time for any grade toxicity considered intolerable by the patient.

Treatment must be interrupted for any CTCAE (v.4) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or Grade 1 or less within 28 days of interruption, the patient may restart treatment with niraparib according to the tables below.

If the event recurs at a similar or worse grade, treatment should be discontinued.

If the toxicity requiring dose interruption has not resolved completely or to CTCAE

Grade 1 during the maximum 4-week (28-day) dose interruption period, the patient must permanently discontinue treatment with niraparib.

Table 2. Cohort 1: Dose Reduction for Nonhematologic Toxicities

Event	**Dose**[1]
Initial dose	100 mg QD
CTCAE Grade 3 or 4 treatment-related SAE/AE ≥ 28 days	Discontinue study treatment

Abbreviations: AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, QD = once daily, SAE = serious adverse event

[1] Dose not to be decreased below 100 mg QD

The dose interruption/modification criteria for hematologic parameters will be based on blood counts and are outlined in Table 4.

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.

If patients present with any of the following symptoms of Posterior Reversible Encephalopathy Syndrome (PRES), seizures, headache, altered mental status, visual disturbance, or cortical blindness (with or without associated hypertension), treatment should be held until neurologic examination and PRES is ruled out. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. In patients with confirmed PRES, treatment must be permanently discontinued.

Table 4: Dose Modification of Niraparib for Hematologic Toxicities

Finding	Modification
Platelet count 75,000-99,999/μL[(1)]	Study treatment must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study treatment may then be resumed at same dose based on clinical judgment.
2nd occurrence of platelet count 75,000-99,999/μL[(1)]	Study treatment must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study treatment may then be resumed at the previous dose.
Platelet count <75,000/μL[(1)]	Study treatment must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study treatment may then be resumed the previous dose.
Neutrophil <1,000/μL[(2)]	Study treatment must be interrupted until neutrophil counts ≥ 1,500/μL, with weekly blood counts for CBC monitored until recovery. Study treatment may then be resumed at previous dose.
Hemoglobin ≤8 g/dL	Study treatment must be interrupted until hemoglobin is ≥ 9 g/dL, with weekly blood counts for CBC monitored until recovery. Study treatment may then be resumed at previous dose.

Abbreviations: CBC = complete blood count

(1) If the platelet count has not reverted within 28 days of interruption to ≥100,000/μL, then the patient should be discontinued.

(2) For patients with platelet count ≤ 10,000/μL, prophylactic platelet transfusion per guidelines may be considered[37,38]. For patients taking anticoagulation or antiplatelet drugs, consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as ≤ 20,000/μL.

In the case of thrombocytopenia, following the first occurrence, resumption of therapy may occur at the same dose when the hematologic toxicity has resolved. If the platelet count has not reverted within 28 days of interruption to ≥100,000/μL, then the patient should be discontinued.

If dose interruption is required at any point on study because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will be also required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume.

Any patient requiring transfusion of platelets or red blood cells (1 or more units) must be removed from the study.

The patient must be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less after 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue study treatment. For major surgery while on treatment, up to

28 days of study treatment interruption is allowed.

All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded.

4.2.5 Packaging, Labeling

Niraparib is supplied by GSK as 100 mg capsules packaged in high-density polyethylene (HDPE) bottles with child-resistant plastic closures. The study treatment will be open-label and will not be patient-specific.

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

4.2.6 Disposal and Destruction

Niraparib will be destroyed at the investigational site, if permitted, according to local regulations.

4.2.7 Previous and Concomitant Medications

Niraparib has shown limited interactions with other drugs. Please refer to Appendix 2.

4.3 Dose-Limiting Toxicity (DLT)

DLT criteria for Adverse Event occurring in Cycle 1 while determining MTD:

1) Grade 3 or higher nonhematologic toxicity, despite adequate treatment, except for Grade 3 rash lasting ≤3 days (all patients should receive topical steroid treatment, oral antihistamines, and oral steroids, if necessary).
2) Grade 3 or greater nausea, vomiting, or diarrhea that persists > 48 hours despite maximal supportive care
3) Grade 4 neutropenia lasting >7 days in the absence of growth factor support.
4) Grade 3 or greater neutropenia of any duration accompanied by fever ≥38.5°C and/or systemic infection.
5) Any other Grade ≥4 hematologic toxicity.
6) Inability to administer at least 75% of planned doses of niraparib due to study drug-related toxicity.
7) Any clinically significant occurrence that the investigator and sponsor agree would place patients at an undue safety risk.

5 STATISTICAL METHODS

The statistical analysis will be mainly descriptive. Continuous variables will be summarized using descriptive statistics: N, mean, standard deviation, median, minimum and maximum. Categorical variables will be presented using frequencies

and percentages. Time-to-event will be described by N, median, range, number censored, and Kaplan-Meier plots.

All data collected on the CRF will be listed on a per-patient basis. There will be no imputations for missing data other than dates. A statistical analysis plan will be finalized prior to analysis. Any deviations from the statistical methods given in the protocol will be described and fully justified in the statistical analysis plan and/or in the final report as appropriate.

Primary objective:

We will estimate the MTD, which is defined as the dose level at which less than one-third of patients will experience a DLT. A traditional dose escalation design will be used, beginning with the lowest dose level and escalating to the maximum allowable dose level as specified in the protocol. Three patients will be treated at a given dose level; a maximum of 4 dosing levels results in a maximum sample size of N=24 patients.

One of the following outcomes will determine the treatment of subsequent patients:

- If none of the three patients experiences a DLT, the next group of patients will be entered in the next higher dose cohort. All patients within a cohort must have completed at least once cycle (28 days) prior to initiation of the next cohort of patients.
- If one of the three patients experiences a DLT, three more patients will be accrued at the current dose level. Subsequently, if only one of the six patients treated at this level experiences a DLT, the dose will be escalated to the next higher dose in the next group of patients. If two or more of the six patients experiences a DLT, the MTD has been exceeded and is defined as the previous dose at which no more than 1/3 experienced a DLT.
- If at least two of the three experience a DLT, the MTD has been exceeded and is defined as the previous dose at which no more than 1/3 experienced a DLT.

If the lowest allowable dose level exceeds the MTD, the study will be terminated and the combination will not be deemed safe for use in this population. Additionally, the highest dose level will not be exceeded, even if no DLTs are experienced at that dose.

Secondary objective 1:

Adverse events will be defined using the CTCAE v. 4.03. We will summarize the AEs overall and by individual AE categories. Serious adverse events will be summarized in a similar manner. These summaries will be performed overall and for each cohort. All events will be summarized as well as the highest grade for each dose cohort. The number of subjects that exhibit a DLT at each dose cohort will be summarized, and a description of the DLT for each subject (if applicable) will be provided.

Secondary objective 2: Individual responses per RECIST criteria 1.1 will be reported if possible. An overall response rate will be calculated for the study population and reported as a frequency.

Tumor Assessment

Radiographic response will be evaluated according to RECIST 1.1 criteria [57] (see Appendix 3) in all patients with measurable disease. Tumor assessments for evaluation of response will be conducted every 8 weeks x 2, and then every 8-12 weeks thereafter until study discontinuation or disease progression, whichever is later. All sites of disease must be evaluated using the baseline assessment methods. Confirmatory assessment of complete response (CR) or partial response (PR) must be performed no less than 4 weeks after the initial documentation of response.

Tumor marker assessments for those patients without measurable disease (GYN only) that had elevated levels on the last prior regimen will be taken at baseline and approximately every 8 ± 2 weeks along with tumor assessments during the study treatment period. All tumor marker assessments must be assayed by the same laboratory for each patient. All target lesions will be measured by consistent imaging techniques throughout the study. The same technique should be used for each evaluation in an individual patient. Results should be recorded in the CRF. Copies of the scans must be available for review. All patients who receive at least two treatment cycles and undergo at least one on-study disease assessment or experience early progression will be considered evaluable for response.

Response Assessment for Gynecologic Patients Without Measurable Disease

Many patients with advanced gynecological malignancies will not have target lesions per RECIST 1.1 due to the nature of the disease. To address this, the Gynecological Cancer Intergroup (GCIG) has reached consensus regarding the criteria for defining progression in clinical trials of recurrent disease, which has been validated and thus accepted in clinical trials[39]. For this study, patients with an ovarian malignancy without target lesions may still be included according to the GCIG consensus guidelines (please see Appendix 3).

5.1 Safety Analyses

Trained study coordinators and/or data managers will enter the information described in this section. All adverse events (AE's) will be presented in incidence tables coded by MedDRA type and body system. Additionally, separate AE incidence tables, coded by MedDRA type, will be presented by: 1) toxicity grade (severity) graded by the Common Terminology Criteria for Adverse Events v4.0 (CTCAE); and 2) relationship to treatment as determined by the investigator/treating physician.

All serious adverse events, discontinuations due to adverse event, or deaths occurring during the course of the trial or within 30 days following termination from the trial will be summarized on a per-patient basis.

Survival information as well as information about patients who have developed MDS/AML will be collected every 8 weeks for at least 2 years from treatment initiation.

5.2 Determination of Sample Size n/a

No power analysis to determine sample size will be done for this study since the primary objective is to determine the maximum tolerated dose of niraparib and everolimus. The sample size will be determined by the dose escalation design of the study.

5.3 Missing Data n/a

No imputation for missing data will be used.

5.4 Interim Analysis n/a

No efficacy analysis is planned. Safety data will be reviewed on an ongoing basis.

6 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

6.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, the principles of Code of Federal Regulations (CFR), ICH GCP and the Declaration of Helsinki as amended in Edinburgh (2000) (Appendix 2).

6.2 Informed Consent

The principles of informed consent and GCP guidelines in FDA-Regulated Clinical Trials are described in the 21 CFR 50, Protection of Human Subjects.

These regulations must be followed in conducting and monitoring clinical investigations. Consent for tumor biopsy and participation in the study will be obtained and documented.

The investigator/physician will thoroughly explain to the patient the purpose and methods of the study, as well as any expected effects and adverse reactions, before any study-specific screening procedures are conducted. The patient will be provided with a copy of the consent and will be given sufficient time and opportunity to inquire about the details of the trial and to decide whether or not to participate. The patient and the person with whom the informed consent is discussed will sign and date the consent form.

The investigator/treating physician will explain that the patient is completely free to refuse to enter the study or to withdraw from it at any time and for any reason. Similarly, the investigator/treating physician and/or Sponsor will be free to withdraw the patient at any time for safety or administrative reasons. Any other requirements necessary for the protection of the human rights of the patient will also be explained, according to current CFR (21, parts 312D, 50 and 56), ICH (ICH E6 1997) and GCP guidelines and the Declaration of Helsinki, 1964 [as amended in Edinburgh (2000)]. A copy of the Declaration of Helsinki is provided in Appendix 8.

6.3 Protocol Approval and Amendment

This study must be approved by an appropriate institutional review board/committee as defined by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1891, Part 56) and the Office of Human Research Protection (45 CFR 46). Prior to screening any patients for participation into this study, the investigator/treating physician must obtain and provide written documentation of IRB review and approval of the protocol and the informed consent document to study sponsor.

The IRB must also be informed of any protocol amendments prior to implementation. The investigator/treating physician must provide reports of any change in research activity (e.g. the completion, termination or discontinuation of the study) to the IRB.

6.4 Subject Confidentiality and Data Protection

Signed consent forms for each subject will be coded with the subject's unique study

identification number and stored locally at the clinical site. Authorization to use the participant's health information will be obtained under the requirements of the federal Health Insurance Portability and Accountability Act (HIPAA). The Authorization will be obtained as part of the informed consent process and will give permission to use health information obtained as part of this research study. The participant may contact us in writing at any time to withdraw their HIPAA authorization, at which point we will not use or provide any health information to researchers and will break the link between the participant's samples and their health information.

Every effort will be made to maintain the confidentiality of information obtained about study participants, however this cannot be guaranteed. Other people may need to see the information. While they will normally maintain the confidentiality of the information, they may not be required to do so by law.

Health information will be used to conduct this study, to determine research results, and possibly develop new tests, procedures, treatments and commercial products. Health information is used to report results of research to federal regulatory agencies. Health information from study participants may be included in an audit to ensure that the study follows regulations, policies, and study plans. To meet regulations, and for reasons related to this research, a copy of informed consent forms and records that identify the study participant may be shared with the following: the Department of Health and Human Services (DHHS); the Food and Drug Administration (FDA); Avera (including physicians, phlebotomists, research staff, data managers, and other associated personnel); and Avera Institutional Review Boards (IRB). All Avera studies will be subject to audit by Avera and/or the DHHS.

All records will be maintained indefinitely unless we receive a written request from the participant or their legally authorized representative requesting that we remove the participant from the study. If informed consent is revoked, we will destroy any samples remaining in the laboratory and remove medical information from the database. Names, birthdates and medical record numbers may be kept to provide a record of past enrollment but all medical record information and other PHI will be deleted. Samples and health information that may have been distributed to researchers prior to receiving the request to withdrawal may continue to be used by the researcher to complete their studies.

6.5 Data Quality Assurance

CRFs will be used to collect the data, and Avera Health will carry out all data management activities. The investigator/treating physician is responsible for maintaining accurate, complete and up-to-date records for each patient. The investigator/treating physician is also responsible for maintaining all source documentation related to the study. All CRFs should be completed in a neat, legible manner to ensure accurate interpretation of the data.

6.6 Access to Source Documents

It is understood that a Clinical Principal Investigator and Clinical Research Associate (CRA) will regularly contact and/or visit the investigator/treating physician, and that the investigator/treating physician (when requested) will allow the CRA to inspect the

study records (CRFs and other pertinent data) and compare patients' medical records with entries in the CRF, provided that patient confidentiality is maintained in accordance with local requirements.

The monitoring and source verification for this study may be conducted remotely and the investigator/treating physician will be required to provide source documents and case report forms via a secure eFax line for this purpose. It will be the CRA's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data on the CRF form. The CRA will monitor the study by comparing patients' medical records with entries in the CRF. The CRA must have access to patient records that are needed to verify the entries on the CRF. By agreeing to participate in this research study, the investigator/treating physician agrees to cooperate with the CRA to ensure that any problems detected in the course of the monitoring visits are resolved.

These records and other relevant data may also be reviewed by appropriate qualified personnel independent from the CRA appointed to audit the study, and by regulatory authorities. Details will remain confidential and patients' names will not be revealed.

6.7 Study Monitoring

It is understood that a Clinical Principal Investigator and Clinical Research Associate (CRA) will regularly contact and/or visit the investigator/treating physician, and that the investigator/treating physician (when requested) will allow the CRA to inspect the study records (CRFs and other pertinent data) and compare patients' medical records with entries in the CRF, provided that patient confidentiality is maintained in accordance with local requirements.

The monitoring and source verification for this study will be conducted remotely and the investigator/treating physician will be required to provide source documents and case report forms via a secure eFax line for this purpose. It will be the CRA's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data on the CRF form. The CRA will monitor the study by comparing patients' medical records with entries in the CRF. The CRA must have access to patient records that are needed to verify the entries on the CRF. By agreeing to participate in this research study, the investigator/treating physician agrees to cooperate with the CRA to ensure that any problems detected in the course of the monitoring visits are resolved.

These records and other relevant data may also be reviewed by appropriate qualified personnel independent from the CRA appointed to audit the study, and by regulatory authorities. Details will remain confidential and patients' names will not be revealed.

6.8 Reporting Product Quality Complaints for Niraparib

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

6.9 Reporting Adverse Events

6.9.1 Recording of Adverse Events

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. AEs will be collected from the time of informed consent to 30 days after last study drug administration. AEs that occur before the first study drug administration, concomitant illnesses, which existed before study entry, but did not worsen during the treatment period and any pre-existing conditions are known as "pre-treatment AEs" and by definition are "unrelated" to study drug. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, electrocardiograms [ECG], reported by patient), must be documented.

The event of disease progression is an efficacy criterion and is therefore not considered an AE. If AEs/SAEs occur in relation to disease progression, the AEs/SAEs must be reported per AE/SAE reporting requirements described in 6.11.3, 6.11.5 and 6.11.7.

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.

6.9.2 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories:

- Seriousness
- Intensity
- Causality

Seriousness and causality should be assessed in accordance with the International Conference on Harmonization's Technical Requirements for Clinical Safety Data Management (E2A Guidelines). Intensity should be assessed in accordance with the

Common Terminology Criteria for Adverse Events (CTCAE v.4)

6.9.3 Reporting Serious Adverse Events (SAEs)

A serious adverse event means that the patient is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe. A serious AE (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s)

Exception: Planned hospitalization (e.g., for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE. Planned hospitalizations should be captured in medical history.

An important medical event may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Investigators must report to the Institution any AE occurring after the signing of informed consent until 30 days following last study drug treatment and within 24 hours of becoming aware of the event.

Sponsor AE and Pregnancy Reporting Information
Dr. Casey Williams Fax: +1-605-322-3299 Telephone: + 1-605-322-3588 Avera Institutional Review Board (IRB) Telephone: +1-605-322-4706

All AEs will be recorded from signing of informed consent until 30 days following study treatment discontinuation. Serious adverse events occurring after this 30-day period and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally related to the investigational drug.

6.9.4 Follow-up of Adverse Events

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

6.9.5 Adverse Events of Special Interest (AESI) for Niraparib

An Adverse Event of Special Interest is defined as 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 to the Sponsor Institution and to GSK is required.

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

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

GSK requires only serious AESI to be reported from Investigator-sponsored studies (ISS). Report serious AESI on SAE Report Forms, as follows:

- MDS and AML along with other secondary cancers should be reported to the Sponsor Institution and to GSK upon awareness for any patient who has received niraparib (regardless of the timeframe since the last dose).
- Pneumonitis should be reported to the Sponsor and to GSK through 90 days after the last dose

6.9.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

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

6.9.7 Pregnancy

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

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

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

An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy on the Pregnancy Outcome Report Form. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

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

6.9.8 Sponsor SAE and Pregnancy Reporting to GSK

The Sponsor Institution must report all SAEs and all follow up information to GSK on a GSK-specific SAE Report Form with accompanying coversheet within 24 hours of becoming aware of the initial event or clinically significant follow-up information.
The Sponsor must provide a causality assessment and must sign and date all SAE Report Forms.

GSK SAE, Serious AESI, and Pregnancy Reporting Information
Send all CIOMS/MedWatch to both: Email: OAX37649@gsk.com Fax: +44(0) 208754 7822

6.10 Investigational Product

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

6.10.1 Dispensing

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

6.10.2 Drug Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatment throughout the clinical study. The study treatment accountability log includes information including the enrollment number, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products

not yet dispensed but will be marked as 'returned' and kept separate from the products not yet dispensed.

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

6.11 Publications

Manuscript submission for publication of the results of this study, or any aspect of work directly related to the study, will be decided by the investigators. Any investigator can submit a publication concept proposal including proposed authorship order to the rest of the investigators for review, which will take place within 30 days after a proposal has been submitted.

7 SCHEDULE OF EVENTS

Table 5. Schedule of Study Assessments

Study Procedures Cycle	Screening Visit	Cycle 1				Cycle 2				Subsequent Cycles	EOT	Post-Treatment Assessme
Day	(≤28 days)	1	8	15	22	1	8	15	22	1	Within 7 days of last dose	Every 8 weeks
Screening												
Written informed consent	X											
Inclusion/Exclusion Criteria	X											
Demographics	X											
Height & Weight	X											
Vital Signs[i]	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status[a]	X	X				X				X		
Medical History & Previous Medications	X											
Physical Exam		X	X	X	X	X				X		
Concomitant medications	X	X				X				X		
Pregnancy Testing[b]	X											
Labs[d] including CBC, BUN and creatinine	X[c]	X	X	X	X	X				X		
Lipid panel	X										X	
Sample collection (whole blood) for molecular and cytogenetic analysis[e]	X										X	
Molecular testing (FoundationOne, CTCs, cfDNA if applicable[f]												
Tumor Assessment	X					After 8 wks and 16 wks of treatment				Every 2-3 cycles		
Treatment												
Adverse Event Monitoring		X	X	X	X	X				X	X	X[g]
TRSC and HRQOL-LASA		X				X				X	X	
Follow-up												
Survival assessment												X
Follow-up for MDS/AML												X
Bone marrow aspirate/biopsy		X[h]										

Footnotes:

a. Performance Status 0-1 (see Appendix 1 – Performance Status).
b. Female subjects of childbearing potential must have a serum beta-hCG pregnancy test that will be performed locally within 3 days prior to study drug administration.
c. Laboratory evaluation at the screening visit must be conducted within 7 days prior to study drug administration.
d. Labs include absolute neutrophil count, platelets, hemoglobin, serum creatinine, total bilirubin, aspartate aminotransferase and alanine aminotransferase.
e. Blood samples collected at screening and EOT will be stored for evaluation if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (e.g., the patient develops MDS/AML). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment.
f. Molecular testing can take place at any time during the study if applicable. Tests will be commercial (not paid for by study) and are not required to participate in the study.
g. AE should be monitored for 30 days after last dose.
h. For any patient diagnosed with MDS/AML while on study, a local hematologist must complete a bone marrow aspirate/biopsy. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid- associated genes). Testing completed as part of standard of care is sufficient as long as the site receives the local hematologist's report. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria) and other sample testing results related to MDS/AML.
i. For Cycle 2, weekly blood pressure monitoring may occur remotely.

8 REFERENCES

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APPENDIX 1 – PERFORMANCE STATUS

ECOG PS	KARNOFSKY PS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

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Available at: http://ecog-acrin.org/resources/ecog-performance-status

APPENDIX 2 – INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Pharmacodynamic interactions

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

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

Pharmacokinetic interactions

Effect of other drugs on niraparib

Substrate of CYPs (CYPA2 and CYP3A4)

Niraparib is a substrate of carboxylesterases (CEs) and UDP-glucuronosyltransferases (UGTs) *in vivo*. Oxidative metabolism of niraparib is minimal *in vivo*. No dose adjustment for niraparib is required when administered concomitantly with drugs known to inhibit or induce CYP enzymes.

Substrate of efflux transporters (P-gp, BCRP, and BESP)

Niraparib is a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).

Niraparib is not a substrate of bile salt export pump (BSEP). The major primary metabolite M1 is not a substrate of P-gp, BCRP, or BESP. No dose adjustment for niraparib is required when administered concomitantly with drugs known to inhibitors of *P-gp, BCRP,* and *BESP efflux* transporters.

Substrate of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)

Neither niraparib nor M1 is a substrate of organic anion transport polypeptide 1B1 (OATP1B1), 1B3 (OATP1B3), or organic cation transporter 1 (OCT1). No dose adjustment for niraparib is required when administered concomitantly with drugs known to inhibitors of *OATP1B1, OATP1B3,* and *OCT1 uptake* transporters.

Substrate of renal uptake transporters (OAT1, OAT3, and OCT2)

Neither niraparib nor M1 is a substrate of organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2). No dose adjustment for niraparib is required when administered concomitantly with drugs known to inhibitors of *OAT1, OAT3,* and *OCT2 uptake* transporters.

Effect of niraparib on other drugs

Inhibition of CYPs (CYPA2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4)

Neither niraparib nor M1 is an inhibitor of any drug-metabolising CYP enzymes, namely CYPA2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

Induction of CYPs (CYPA2 and CYP3A4)

Neither niraparib nor M1 is a CYP3A4 inducer. Niraparib weakly induces CYP1A2 in vitro. However, a clinically meaningful drug interaction via an induction of CYP3A4 or CYP1A2 is unlikely. M1 is not a CYP1A2 inducer.

Inhibition of efflux transporters (P-gp, BCRP, and BESP)

Niraparib is not an inhibitor of P-gp or BSEP. Niraparib is a weak inhibitor of BCRP in vitro. However, a clinically meaningful drug interaction via an inhibition of BCRP is unlikely. The major primary metabolite M1 does not appear to be an inhibitor of P-gp, BCRP, or BESP.

Inhibition of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)

Neither niraparib nor M1 is an inhibitor of organic anion transport polypeptide 1B1 (OATP1B1), 1B3 (OATP1B3), or organic cation transporter 1 (OCT1).

Inhibition of renal uptake transporters (OAT1, OAT3, and OCT2)

Neither niraparib nor M1 is an inhibitor of organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2).

Moderate CYP3A4 Inhibitors		
amprenavir	darunavir/ritonavir	fosamprenavir
aprepitant	diltiazem	grapefruit juice (a)
atazanavir	erythromycin	imatinib
ciprofloxacin	fluconazole	verapamil
Strong CYP3A4 Inhibitors		
boceprevir	ketoconazole	ritonavir
clarithromycin	lopinavir/ritonavir	saquinavir
conivaptan	mibefradil (b)	telaprevir
grapefruit juice (a)	nefazodone	telithromycin
indinavir	nelfinavir	voriconazole
itraconazole	posaconazole	
Clinically Significant Enzyme Inducers		
carbamazepine	rifabutin	St. Johns Wort
phenobarbital	rifampin	
phenytoin	rifapentine	

Source:
fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.html

APPENDIX 3 – CRITERIA FOR PROGRESSIVE DISEASE

Adapted from: Revised Response Evaluation Criteria in Solid Tumors (RECIST)

Criteria; Version 1.1, 200927

All subjects who have received a minimum of 2 cycles of study treatment will be considered evaluable for response. All subjects who develop early progressive disease (regardless of the duration of the study treatment) prior to response evaluation will be considered to have progressed on study.

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is a primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion.

A measurable lesion is defined as a lesion that can be accurately measured by CT scan in at least one dimension (longest diameter to be recorded) as ≥ 10 mm. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology. A tumor lesion that is situated in a previously irradiated area is eligible for measurable disease provided: 1) there has been documented disease progression in this site; 2) the criteria for measurability as outlined above are met; 3) it is not the only site of measurable disease.

Lesions that are considered non-measurable include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, and abdominal masses that are not confirmed and followed by imaging techniques. Previously irradiated lesions will be considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Baseline Documentation of Target and Non-Target Lesions

Baseline documentation of tumor sites may include imaging assessment of disease in the chest, abdomen, and pelvis. A baseline imaging study of the brain is not required unless there is a prior history of brain metastasis or the subject has neurological symptoms. All baseline tumor measurements must be documented within 1 month prior to start of therapy. Repeat tumor measurements will be required after every 2 cycles of study? Or after 3 cycles of therapy? If there is reduction in tumor size consistent with a complete response (CR) or a partial response (PR), or stabilization in the tumor size consistent with stable disease (SD), tumor evaluation will be repeated in 4 weeks to allow for confirmation of the tumor status (changed from response). Subsequent tumor evaluations will then be performed after every 2 cycles.

Target Lesions

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

Non-Target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", "increased", or "decreased."

Tumor Response Criteria

Evaluation of Target Lesions

Complete response (CR): Disappearance of all target lesions. Must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met.

Partial response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met.
Progression (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum of diameters recorded since the treatment started (and the sum must demonstrate an absolute increase of at least 5 mm) or the appearance of one or more new lesions.
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest sum of diameters since the treatment started. Must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for stable disease are first met.

Evaluation of Non-target Lesions

Complete response (CR):	Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis)
Non-complete response (non-CR):	Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.
Progression (PD):	Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.*

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

Note: If tumor markers are initially above the ULN, they must normalize for that subject to be considered in CR.

If measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology or histology. In rare cases, such techniques can be used to differentiate between PR and CR (i.e., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors may remain).

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

Evaluation of Best Overall Response

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

DETERMINATION OF BEST OVERALL RESPONSE			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Conditions that may define "early progression, early death, and inevaluability" are study-specific and should be clearly defined in each protocol (depending on treatment duration, treatment periodicity).

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

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation using calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of treatment.

Note: Tumor lesions in a previously irradiated area are not optimally considered measurable disease. If the investigator/treating physician thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended.

Lesions on chest radiographs are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Computerized tomography (CT) is preferable.

Cross-sectional imaging (conventional CT and MRI) should be performed, with contiguous cuts ≤ 10 mm in thickness. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm; this applies to the chest, abdomen, and pelvis (head, neck, and extremities usually require specific imaging protocols).

Ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible, when the primary endpoint of a study is objective response evaluation. It is a possible alternative to clinical measurement of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm complete disappearance of superficial lesions usually assessed by clinical evaluation.

Confirmatory Measurement/Duration of Response

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies performed no less than 4 weeks after the criteria for

response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at an interval of 4 weeks.

Duration of Response

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

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

Duration of Stable Disease

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

Time to Disease Progression

Defined as the time from the date of enrollment/randomization to date of progression as assessed by the conventional response criteria, death, or the start of further antitumor therapy. Subjects lost to follow-up will be censored at their last known alive date.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub- analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

The 95% confidence intervals should be provided.

Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 - Consensus by the Gynecological Cancer Intergroup (GCIG)

The following two scenarios will be accepted for gynecological patients according to the GCIG definitions as cited in [34]:

Table 2. Recommendations according to GCIG for CA 125 criteria for response and progression [60].

	Use Recommended by GCIG
Relapse trials	CA 125 response and progression

Definition of Response According to CA 125

At least a 50% reduction in CA 125 levels from the pretreatment sample must be achieved in order to be considered a CA 125 response, which must be confirmed and maintained for at least 28 days. The pretreatment CA 125 must be at least twice the upper limit of the reference range and within 2 weeks before initiating treatment in order to evaluate a patient based on this criteria. Additionally, the following rules will apply:

- If the sample shows a 50% reduction in CA 125 levels, the 28 day confirmatory sample must be less than or equal to the previous sample (an assay variability of 10% is allowed)
- Variations within the reference range of CA 125 levels will not interfere with the definition of response.
- The same assay method must be used for each patient, and the assay must routinely undergo quality control testing
- If the patient is receiving a mouse antibody then they are not considered to be evaluable by CA 125 unless there is data to support that the assay is not influenced by human anti-mouse antibody.
- If there has been medical or surgical interference with the patient's pleura or peritoneum during the previous 28 days then the patient is not considered to be evaluable by CA 125
- If therapy has included 2 treatment modalities (e.g. surgery and chemotherapy and/or targeted therapy) then the CA 125 cannot distinguish between the effects of the modalities
- The date that the CA 125 level is first reduced by 50% will be the date of the CA 125 response

Definition of Progression According to CA 125

If non-target lesions are present by radiological imaging, then the following will be used to evaluate best overall response

Table 3. Evaluation of best overall response in patients without measurable disease but are evaluable by CA 125 [60].

CA 125	Nontarget Lesions	New Lesions	Overall Serological Response	Best Response Also Requires
Response and normalized	CR	No	CR	Confirmed and maintained for at least 28
Response	Non-PD	No	PR	
Normalized but no response	Non-CR/Non-PD	No	SD	
Non-PR/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

For patients that have measurable disease per RECIST 1.1 and CA 125 criteria, responses should be determined according to the following table.

Table 4. Best overall response combining RECIST 1.1 and CA 125 [60].

Target Lesion	Nontarget	New Lesion	CA 125	Overall Best Response
CR	CR	No	Normal	CR
CR	Non-CR, Non-PD	No	Not PD	PR
CR	CR	No	PR but not	PR
CR	Not evaluated	No	PR	PR
PR	Non-PD or Not evaluated	No	Not PD	PR
Not evaluated	Non-PD	No	PR	PR
PD or new lesion >28 days from CA 125 PR			PR	PR
SD	Non-PD	No	PR	PR
SD	Non-PD or Not Evaluated	No	Not PR and Not PD	SD
PD or new lesion ≤28 days from CA 125 PR			PR	PD
PD	Any	Yes or No	Any	PD
Any	PD	Yes or No	Any	PD
Any	Any	Yes	Any	PD
Any	Any	Yes or No	PD	PD

If both the RECIST 1.1 and CA 125 response criteria are used, the date of response will be defined as the date of the earlier of the two events if combined response reporting is to be used. Also, the best response for CR and PR also requires confirmation and maintenance for at least 28 days.

APPENDIX 4 – THERAPY-RELATED SYMPTOMS CHECKLIST (TRSC)

Name: Hospital # Date:

PLEASE CHECK THE PROBLEMS YOU HAVE HAD IMMEDIATELY AFTER AND SINCE YOUR LAST TREATMENT.
PLEASE CIRCLE HOW SEVERE THE PROBLEM WAS ACCORDING TO THE FOLLOWING SCALE:

0 = NONE 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE

CHECK	EXAMPLE	Degree of Severity (CIRCLE)				
□□	**Pain**	**0**	**1**	**2**	□□	**4**
□□	Taste Change	0	1	2	3	4
□□	Loss of appetite	0	1	2	3	4
□□	Nausea	0	1	2	3	4
□□	Vomiting	0	1	2	3	4
v □□	Weight loss	0	1	2	3	4
□□	Sore mouth	0	1	2	3	4
□□	Cough	0	1	2	3	4
□□	Sore throat	0	1	2	3	4
□□	Difficulty swallowing	0	1	2	3	4
□□	Jaw pain	0	1	2	3	4
□□	Shortness of breath	0	1	2	3	4
□□	Numbness in fingers and/or toes	0	1	2	3	4
□□	Feeling sluggish	0	1	2	3	4
□□	Depression	0	1	2	3	4
□□	Difficulty concentrating	0	1	2	3	4
□□	Fever	0	1	2	3	4
□□	Bruising	0	1	2	3	4
□□	Bleeding	0	1	2	3	4
□□	Hair loss	0	1	2	3	4
□□	Skin changes	0	1	2	3	4
□□	Soreness in vein where chemotherapy was given	0	1	2	3	4
□□	Difficulty sleeping	0	1	2	3	4
□□	Pain	0	1	2	3	4
□□	Decreased interest in sexual activity	0	1	2	3	4
□□	Constipation	0	1	2	3	4
	Other problems (please list below)					
□□		0	1	2	3	4
□□		0	1	2	3	4
□□		0	1	2	3	4
□□		0	1	2	3	4

APPENDIX 5 – WHO MDS CLASSIFICATION CRITERIA

The 2008 World Health Organization (WHO) classification of myelodysplastic syndromes (MDS),[1] as well as the International Prognostic Scoring System (IPSS), are provided below.[2]

Myelodysplastic syndromes are a group of clonal myeloid neoplasms characterized by ineffective hematopoiesis that present clinically as cytopenia(s), dysplasia in one or more hematopoietic cell lines in the bone marrow, and risk of transformation to acute myeloid leukemia (AML)

The WHO classification system of MDS relies on incorporating clinical features, peripheral blood and bone marrow findings, and cytogenetic analysis.[1] This classification also includes a collection of heterogeneous neoplasms that share features of MDS and myeloproliferative neoplasms.

Refractory cytopenia with unilineage dysplasia (RCUD):

Blood: single cytopenia or bicytopenia

Bone marrow: dysplasia in ≥ 10% of 1 cell line, < 5% blasts

Refractory anemia with ring sideroblasts (RARS):

Blood: anemia, no blasts

Bone marrow: ≥ 15% of erythroid precursors with ring sideroblasts, erythroid dysplasia only, < 5% blasts

Refractory cytopenia with multilineage dysplasia (RCMD):

Blood: cytopenia(s), < 1 × 10^9/L monocytes

Bone marrow: dysplasia in ≥ 10% of cells in ≥ 2 hematopoietic lineages, ±15% ring sideroblasts, < 5% blasts

Refractory anemia with excess blasts-1 (RAEB-1):

Blood: cytopenia(s) ≥ 2-4% blasts, < 1 × 10^9/L monocytes

Bone marrow: unilineage or multilineage dysplasia, no Auer rods, 5-9% blasts

Refractory anemia with excess blasts-2 (RAEB-2):

Blood: cytopenia(s), 5-19% blasts, < 1 × 10^9/L monocytes

Bone marrow: unilineage or multilineage dysplasia, Auer rods, ± 10-19% blasts

Myelodysplastic syndrome – unclassified (MDS-U):

Blood: cytopenias

Bone marrow: unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts

MDS associated with isolated del(5q):

Blood: anemia, platelet levels normal or increased

Bone marrow: unilineage erythroid dysplasia, isolated del(5q), < 5% blasts

Therapy-related MDS (t-MDS):

Blood and bone marrow findings of 1 of the above diagnostic categories (frequently with multilineage dysplasia)

Previous history of exposure to cytotoxic chemotherapy and/or radiation therapy administered for treatment of cancer or non-neoplastic disease

2008 WHO terminology: therapy-related myeloid neoplasm

APPENDIX 6 – HEALTH-RELATED QUALITY OF LIFE (HRQOL), LINEAR ANALOGUE SELF-ASSESSMENT (LASA)

Patient Name:_____xxxxxx_____ Date:

_____

Patient Number: _____

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings during the past week, including today.

How would you describe:

1. **your overall Quality of Life?**

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

2. **your overall mental (intellectual) well being?**

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

3. **your overall physical well being?**

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

4. **your overall emotional well being?**

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

5. **your level of social activity?**

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

6. **your overall spiritual well being?**

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX 7 – DECLARATION OF HELSINKI

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research that ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best

proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research investigators/treating physician should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator/treating physician, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has

the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed participants in the research project.

12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the

impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well- informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator/treating physician must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator/treating physician must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators/treating physicians are obliged to

preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. . The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX 8 – SAFETY REPORTING INFORMATION

Submission of Reports

A central contact at the coordinating institution will forward all treatment emergent Serious Adverse Event (SAE) reports regardless of causality, to GSK within 24 hours of completion of the final report. The institution will forward both initial and follow-up versions of each SAE report. The Institution will also provide reports for all pregnancies in the same manner.

Format of SAE Reports

All SAEs should be provided to GSK on a CIOMS I form; copies of the institution's SAE form are not sufficient for reporting to GSK. Exact content should be entered directly from the institution's SAE form into the CIOMS I format. Incomplete CIOMS I forms are acceptable.

- For expected and/or unrelated events, it is not necessary to include a narrative.
- For Suspected Unexpected Serious Adverse Reactions (SUSARs), please provide a comprehensive narrative for all events.

GSK SAE and Pregnancy Reporting Information
Drug Safety Alliance / Ashfield Pharmacovigilance
Send all CIOMS/MedWatch to both: Email: OAX37649@gsk.com Fax: +44(0) 208754 7822

SUSAR Distribution

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

APPENDIX 9 – Health Related Quality of Life Assessment

HEALTH-RELATED QUALITY OF LIFE (HRQOL), LINEAR ANALOGUE SELF ASSESSMENT (LASA)

Patient Name: _____ Date: _____

Patient Number: _____

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

How would you describe:

1. your overall Quality of Life?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be — As good as it can be

2. your overall mental (intellectual) well being?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be — As good as it can be

3. your overall physical well being?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be — As good as it can be

4. your overall emotional well being?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be — As good as it can be

5. your level of social activity?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be — As good as it can be

6. your overall spiritual well being?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be — As good as it can be

APPENDIX 10 – Therapy Related Symptoms Checklist

THERAPY-RELATED SYMPTOMS CHECKLIST (TRSC)

Name: _____ Hospital #_____ Date:_____

PLEASE **CHECK** THE PROBLEMS YOU HAVE HAD IMMEDIATELY AFTER AND SINCE YOUR LAST TREATMENT. PLEASE CIRCLE HOW SEVERE THE PROBLEM WAS ACCORDING TO THE FOLLOWING SCALE:

0 = NONE 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE

CHECK	EXAMPLE	Degree of Severity **(CIRCLE)**				
☒	Pain	0	1	2	3	4
☐	Taste Change	0	1	2	3	4
☐	Loss of appetite	0	1	2	3	4
☐	Nausea	0	1	2	3	4
☐	Vomiting	0	1	2	3	4
☐	Weight loss	0	1	2	3	4
☐	Sore mouth	0	1	2	3	4
☐	Cough	0	1	2	3	4
☐	Sore throat	0	1	2	3	4
☐	Difficulty swallowing	0	1	2	3	4
☐	Jaw pain	0	1	2	3	4
☐	Shortness of breath	0	1	2	3	4
☐	Numbness in fingers and/or toes	0	1	2	3	4
☐	Feeling sluggish	0	1	2	3	4
☐	Depression	0	1	2	3	4
☐	Difficulty concentrating	0	1	2	3	4
☐	Fever	0	1	2	3	4
☐	Bruising	0	1	2	3	4
☐	Bleeding	0	1	2	3	4
☐	Hair loss	0	1	2	3	4
☐	Skin changes	0	1	2	3	4
☐	Soreness in vein where chemotherapy was given	0	1	2	3	4
☐	Difficulty sleeping	0	1	2	3	4
☐	Pain	0	1	2	3	4
☐	Decreased interest in sexual activity	0	1	2	3	4
☐	Constipation	0	1	2	3	4
	Other problems (please list below)					
☐		0	1	2	3	4
☐		0	1	2	3	4
☐		0	1	2	3	4
☐		0	1	2	3	4