A Phase II Study of Niraparib in Combination with EGFR Inhibitor Panitumumab in patients with advanced colorectal cancer

Sponsor:	Olatunji Alese, MD
Principal Investigator:	Olatunji Alese, MD
Study Drug Name:	Niraparib, Panitumumab
Clinical Phase:	II
Number of Subjects:	26
IND Number:	IND 142710
EudraCT Number:	N/A
Date of Original Protocol:	8 January 2019
Date of Current Protocol:	27 October 2021
Version:	02

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.

LIST OF STUDY CONTACTS

Sponsor

Winship Cancer Institute
Emory University
1365C Clifton Road NE,
Atlanta, GA 30322

Principal Investigator:

Olatunji Alese, MD
Winship Cancer Institute
1365C Clifton Road NE,
Atlanta, GA 30322

Phone: 404 778 1900
Email: oalese@emory.edu

Co-Principal Investigator:

Bassel El-Rayes, MD
Winship Cancer Institute
1365C Clifton Road NE,
Atlanta, GA 30322

Phone: 404 778 1900
Email: bassel.el-rayes@emoryhealthcare.org

Co- Investigators

Christina Wu, MD
Walid Shaib, MD
Mehmet Akce, MD
Maria Diab, MD
Olumide Gbolahan, MD
Stephen Szabo, MD
Sarah Friend, MD
Neela Natarajan, MD

Study Coordinators: TBD

Biostatistician:

Yuan Liu, Ph.D.
Research Associate Professor
Biostatistics Shared Resource at Winship Cancer Institute
Phone: 404-778-1989
Email: YLIU31@emory.edu

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Phase II Study of Niraparib in Combination with EGFR Inhibitor Panitumumab in patients with advanced colorectal 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.

_____ _____

Olatunji Alese, MD Date
Associate Professor
Winship Cancer Institute of Emory University

INVESTIGATOR SIGNATURE PAGE

Declaration of the Investigator

Title: A Phase II Study of Niraparib in Combination with EGFR Inhibitor Panitumumab in patients with advanced colorectal 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

_____ _____

[Name] **Date**
[Title]
[Institution]

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS

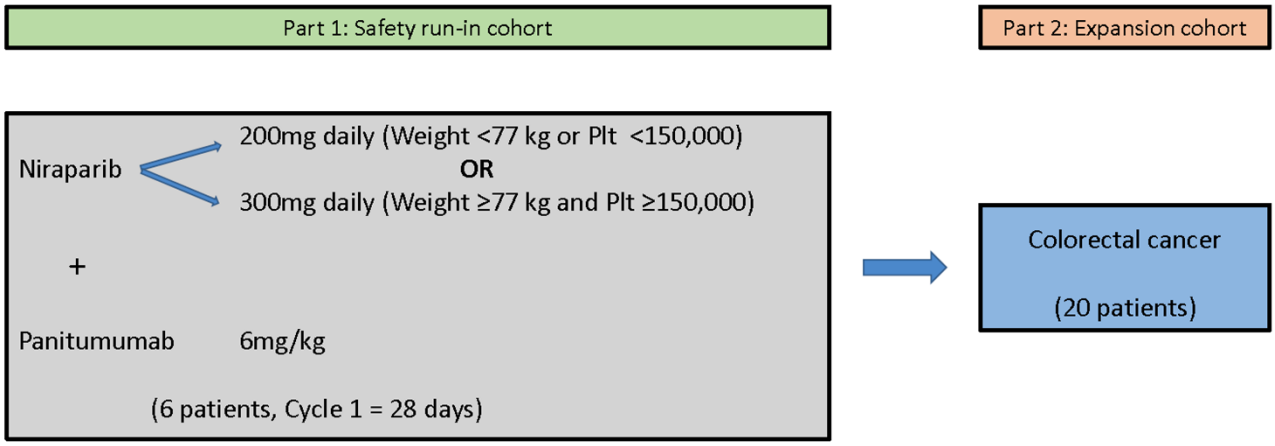
Table 1 List of Abbreviations

Abbreviation	Definition
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse even of special interest
AML	acute myeloid leukemia
AUC	area under the curve
BER	base excision repair
BRCA	breast cancer gene
CBC	complete blood count
CL	oral clearance
CRC	Colorectal cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DDR	DNA damage repair
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
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
irAEIs	immune-related adverse events of interest
IUD	intrauterine device
LLN	Lower limit of normal
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

Abbreviation	Definition
NHEJ	non-homologous end joining
ORR	Objective response rate
OS	Overall survival
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
QTc	corrected QT interval
RAS	Rat sarcoma gene
SAE	serious adverse event
TEAS	treatment-emergent adverse events
ULN	upper limit of normal
WT	Wild type

1 INTRODUCTION

1.1 Study Design



Dose level	Niraparib (mg daily)	Panitumumab (IV Q2w)	Number of patients
Safety run-in	300mg (body wt. ≥77kg and platelets ≥150,000 µL) **OR** 200 mg (body wt. <77kg or platelets <150,000 µL)	6mg/kg	6

Additional 20 CRC patients with the same inclusion criteria will be subsequently enrolled and treated to determine efficacy. Patients who fail screening will be replaced on the study.

1.2 Primary Objective:

Evaluate the activity of the combination of Niraparib with EGFR Inhibitor Panitumumab in previously treated patients with RAS WT metastatic colorectal cancer.

Hypothesis: The combination of Niraparib and Panitumumab will be safe, tolerable and effective in patients with advanced RAS WT colorectal cancer.

1.3 Secondary Objectives

I. Define the toxicity profile of the combination of Niraparib and Panitumumab. The additional patients enrolled on the expansion cohorts will help confirm the toxicity profile.

II. Evaluate the activity of the combination of Niraparib and Panitumumab in previously treated patients with metastatic colorectal cancer.

1.4 Endpoints

The primary endpoint of this phase II study will be clinical benefit rate = Complete Response + Partial Response + Stable disease (CR +PR + SD) rate.

The other secondary end points include:

A. Toxicity profile of the combination of Panitumumab and Niraparib; additional patients enrolled on the expansion cohort to confirm the toxicity profile.

B. Efficacy endpoints: Objective response rate, response duration, overall survival and progression free survival. This will only be preliminary data since this is a secondary objective.

C. Biomarker analysis: Objective of the correlative assays is to try and identify patients who respond to the combination. As a standard of care at Emory, patients with stage IV CRC receive genomic profiling to evaluate for therapeutic targets. We propose analyzing these profiles to identify patients with defects in their DNA repair pathways as a potential biomarker for this regimen. Normal skin biopsies from regions that contained hair follicles will be obtained in the form of a 4-mm diameter punch biopsy (8 mm depth) before treatment and on days 22 of cycle 1. The biopsies will be evaluated for:

   1. Four metrics of cytotoxicity - Caspace-3, γ-H2AX, PARP, MAPK, together with indicators of EGFR downregulation.

   2. Tumor infiltrating cells using multiplex immunofluorescence panels.

2 BACKGROUND AND SIGNIFICANCE

2.1 Background of PARP and Homologous Recombination Deficiency

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

Activated PARP catalyzes the addition of long polymers of adenosine diphosphate (ADP)-ribose onto PARP and several other proteins associated with chromatin, including histones and various DNA repair proteins.[2,3] This results in chromatin relaxation, fast recruitment of DNA repair proteins, and efficient repair of DNA breaks. In this manner, PARP plays a key role in sensing DNA damage and converting it into intracellular signals that activate the base excision repair (BER) and single-strand break repair pathways. Normal cells repair up to 10,000 DNA defects daily, and single-strand breaks are the most common form of DNA damage. Cells that are unable to repair this burden of DNA damage, such as those with defects in the homologous recombination or BER pathways, are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. They enter the S phase (DNA replication) of the cell cycle with unrepaired single- and double-strand breaks. Pre-existing single-strand breaks are converted to double-strand breaks as the replication machinery passes. Accumulated double-strand breaks present during S phase are repaired by homologous recombination. Homologous recombination is the preferred repair pathway because it is associated with a much lower error rate than other forms of repair. Cells that are unable to perform DNA repair via homologous recombination (e.g., due to inactivation of genes required for homologous recombination, such as breast cancer [*BRCA1*]- or breast cancer 2 [*BRCA2*]-mutated cells) are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. These cells accumulate stalled replication forks during S phase and are more likely to use the error-prone nonhomologous end joining (NHEJ) or alternative (alt)-NHEJ pathways to repair double-strand breaks in DNA. Accumulation of errors in DNA by NHEJ contributes to mutation burden that promotes the development of cancer. Over time, the buildup of excessive DNA errors in combination with the inability to complete S phase (because of stalled replication forks) contributes to cell death.[2,3]

Treatment with PARP inhibitors could represent a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline *BRCA* mutation (g*BRCA*mut) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on NHEJ, alt-NHEJ, and BER for maintenance of genomic integrity. PARP inhibitors block alt-NHEJ and BER, forcing tumors with BRCA deficiencies to use the error-prone NHEJ to fix double-strand breaks.[1] Non-*BRCA* deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors.[4] The rationale for anticancer activity in a subset of non-g*BRCA*mut tumors is that they share distinctive DNA repair defects with g*BRCA*mut carriers, a phenomenon broadly described as "BRCAness."[5] 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.[6] A subset of these tumors had biologically plausible molecular alterations that may make them sensitive to PARP inhibition by niraparib. A similar analysis of triple-negative breast cancer indicates that 43% to 44% of these patients have tumors with homologous recombination defects.[7] Homologous recombination is a complex pathway, and several genes other than *BRCA1* and *BRCA2* are required either to sense or repair DNA double-strand breaks via the homologous recombination pathway. Therefore, PARP inhibitors are also selectively cytotoxic for cancer cells with deficiencies in DNA repair proteins other than *BRCA1* and *BRCA2*.[1,5,8]

Recent clinical studies have shown PARP inhibitors to be active in breast and ovarian cancer. Clinical anticancer activity with PARP inhibitors has been seen in both patients with g*BRCA*mut and without g*BRCA*mut; however, activity is more robust in patients with the germline mutation.[1,4,9-15] In summary, treatment with PARP1/2 inhibitors represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair. Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of the tumor cells than that of normal cells.

2.2 Background of Niraparib

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

2.2.1 Nonclinical Experience

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

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

2.2.2 Clinical Experience

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

Phase 1 Study of Niraparib Monotherapy in Advanced Solid Tumors

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

Phase 1 Study of Niraparib Monotherapy in Advanced Solid Tumors

Clinical activity data for niraparib administered as monotherapy in patients with ovarian cancer are available from 1 early-phase clinical study. In Parts A and B of the Phase 1 study PN001 (ClinicalTrials.gov identifiers: MK-4827-001 and 2008_501), 100 patients with advanced solid tumors who had received a median of 3 prior therapies were enrolled; 49 patients had ovarian cancer (13 platinum-sensitive, 35 platinum-resistant, and 1 platinum-refractory).[11] An additional 4 patients were enrolled in Part D of the study, which assessed pharmacokinetics only.[16]

The most common nonhematological TEAEs were nausea, fatigue, anorexia, constipation, vomiting, and insomnia. These TEAEs were mainly mild to moderate in severity, self-limiting, and manageable with standard treatments. Hematological toxicity appeared to be dose proportional and most frequently arose in the setting of cumulative doses. Anemia was reported in 48 (48%) of 100 patients and was Grade ≥3 in 10 (10%) of 100 patients. Thrombocytopenia was less common (35 [35%] of 100 patients) and was Grade ≥3 in 15 (15%) of 100 patients. Neutropenia was the least commonly reported (24 [24%] of 100 patients), and was Grade 3 in 4 (4%) of 100 patients at niraparib doses of 300 and 400 mg. In all cases, hematological TEAEs were uncomplicated and reversible. Twenty patients required dose reductions (usually by 1 dose level) for recurrent anemia or thrombocytopenia. Treatment was discontinued due to AEs in 7 patients, including the 4 patients who had DLTs during the first cycle and 3 patients who had Grade 3 vomiting, Grade 2 prolongation of QT interval, and Grade 3 prolongation of QT interval. No treatment-related deaths occurred.

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

Phase 3 Study of Niraparib Monotherapy in Platinum-sensitive, Recurrent Ovarian Cancer

In the randomized, double-blind, Phase 3 NOVA trial (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer), a total of 553 patients were randomized at 107 centers worldwide[13]. Patients were categorized according to the presence or absence of a g*BRCA*mut (g*BRCA* cohort and non-g*BRCA* cohort) within their tumors and the type of non-g*BRCA*mut and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily (QD). The primary end point was PFS. The study enrolled 203 patients in the g*BRCA*mut cohort and 350 patients in the non-g*BRCA*mut cohort. Among the 350 patients in the non-g*BRCA*mut cohort, 162 had tumors that were identified as homologous recombination deficiency positive (HRDpos), and 134 had tumors that were HRD negative (HRDneg). HRD status was not determined for 54 patients.

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

Table 1: Progression-Free Survival in Ovarian Cancer Patients in NOVA

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

Source: PR-30-5011-C (NOVA main) CSR
Abbreviation: CI = confidence interval; CSR = clinical study report; gBRCAmut = germline BRCA mutation; HR = hazard ratio; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; NE = not evaluated; PFS = progression-free survival.
[a] PFS is defined as the time in months from the date of randomization to progression or death.
[b] Based on stratified log-rank test using randomization stratification factors.
[c] Based on the stratified Cox proportional hazards model using randomization stratification factors.

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

All 367 patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). The high rate of TEAEs in the placebo group indicates the burden of prior chemotherapy and the patient's underlying ovarian cancer. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*mut and non-g*BRCA*mut

cohorts. In the overall safety population, for the niraparib versus placebo treatment arms, the incidences of Grade 3 or 4 TEAEs (74% vs. 23%), serious adverse events (SAEs) (30% vs. 15%), TEAEs leading to treatment interruption (67% vs. 15%), TEAEs leading to dose reduction (69% vs. 5%), and TEAEs leading to treatment discontinuation (15% vs. 2%) were higher for niraparib than for placebo. There were no on-treatment deaths reported.

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

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib. In the Phase 3 NOVA study, the incidence of MDS/AML in patients who received niraparib (5 of 367; 1.4%) was similar to its incidence in patients who received placebo (2 of 179; 1.1%). Guidance on monitoring patients for new AEs of MDS/AML and the follow-up of patients with suspected MDS/AML is provided.

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

Baseline Platelet Count and Weight as Predictors of Thrombocytopenia.

An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase I study, PN001. This analysis determined that baseline platelets had an impact on platelet nadir; lower baseline platelets (<180 10^9/L) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76%) or Grade ≥ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body

weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, Grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24%) compared to patients in the highest quartile (10%).

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

Finally, a classification tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing ≥Grade 3 thrombocytopenia within 30 days after the first dose of niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg **or** baseline platelet count <150,000 µL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of patients with a body weight >77 kg **and** a platelet count >150,000 µL. Further, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000 µL and was only 206 mg for patients with body weight < 77 kg or platelet count <150,000 µL. Thus, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. These observations are to be confirmed in the present study with the inclusion of study treatment dosed at 200 mg (2 capsules of niraparib or placebo) in patients whose baseline weight is <77 kg or baseline platelet count is <150,000 µL.

2.3 Rationale for Current Study

2.3.1 Rationale for Study Population

Each year, an estimated 300,000 people are diagnosed with GI cancers, with over 150, 000 people dying annually[17]. Almost 135,000 cases of colorectal cancer (CRC) are projected to be diagnosed in the US in 2017; with more than 50,000 deaths from the disease. CRC is the second leading causes of cancer death in both sexes the US. Therefore, GI cancers are a major area of need for new drug development.

Panitumumab (Vectibix) is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR), and is indicated as a single agent for the treatment of metastatic colorectal carcinoma[18]. The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine

kinases, including EGFR, HER2, HER3, and HER4. EGFR is constitutively expressed in normal epithelial tissues, including the skin and hair follicle. EGFR is over-expressed in certain human cancers, including colon and rectum cancers. Interaction of EGFR with its normal ligands (eg, EGF, transforming growth factor-alpha) leads to phosphorylation and activation of a series of intracellular proteins, which in turn regulate transcription of genes involved with cellular growth and survival, motility, and proliferation. Signal transduction through the EGFR results in activation of the wild-type KRAS protein. However, in cells with activating KRAS somatic mutations, the mutant KRAS protein is continuously active and appears independent of EGFR regulation.

Panitumumab binds specifically to EGFR on both normal and tumor cells, and competitively inhibits the binding of ligands for EGFR[19]. Nonclinical studies show that binding of panitumumab to the EGFR prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased proinflammatory cytokine and vascular growth factor production, and internalization of the EGFR. In vitro assays and in vivo animal studies demonstrate that panitumumab inhibits the growth and survival of selected human tumor cell lines expressing EGFR.

Safety data are available from 15 clinical trials in which 1467 patients received Panitumumab; of these, 1293 received Panitumumab monotherapy and 174 received Panitumumab in combination with chemotherapy[19-22]. Overall Panitumumab is well tolerated. Most common adverse reactions (≥ 20%) are skin toxicities (i.e., erythema, dermatitis acneiform, pruritus, exfoliation, rash, and fissures), paronychia, hypomagnesemia, fatigue, abdominal pain, nausea, diarrhea, and constipation. Niraparib is an orally active poly(ADP-ribose) polymerase (PARP)–1 and –2 inhibitor. It is well tolerated as a single agent and has no overlapping toxicity with Panitumumab.

Colorectal cancer is treated both in the curative and metastatic settings with oxaliplatin-fluoropyrimidine combinations. The efficacy of these regimens and the sensitivity of CRC to the platinum compound have been established in numerous preclinical and clinical studies, highlighting the role of such first line chemotherapy combinations in clinical practice[23-26]. Moreover, numerous DNA repair genes have been demonstrated to play significant roles in the development and propagation of colorectal cancer in both genetic and sporadic cases. Apart from the well described heritable factors with known hereditary syndromes such as mismatch repair genes in Lynch syndrome, several lower penetrance polymorphisms affect other DNA repair genes. DNA repair pathways, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), direct reversal repair (DRR), and double-strand break repair are complex, evolutionarily conserved, and critical in carcinogenesis[27]. A previous study identified 61 polymorphisms in 26 different DNA repair genes associated with CRC.

A major consideration in the treatment of different malignancies with PARP inhibition as discussed in section 2.1 above is the correlation with platinum sensitivity. Cancer cell sensitivity and resistance to both PARP inhibition and platinum have been associated with

loss and restoration of HR DNA repair, respectively, indicating similar mechanisms of anticancer activity and resistance[28,29]. Platinum sensitivity in CRC could therefore predict for anticancer properties of PARP inhibition when utilized in the setting of synthetic lethality.

Preliminary data have shown that EGFR inhibition induces synthetic lethality with PARPi in head and neck squamous cell carcinomas (HNSCCs) in vitro by attenuating DNA repair pathways. Combined EGFR and PARP inhibition resulted in the greatest tumor growth delay versus either agent alone in mice bearing head and neck tumor xenografts, correlated with persistent γ-H2AX foci indicative of unresolved DNA damage. This susceptibility to PARPi induced by EGFR inhibition was associated with deficient NHEJ- and HR-mediated DNA repair and subsequent persistence of DNA damage.

In addition, regulation of homologous recombination repair involving EGFR and BRCA1 interaction, and alteration of subcellular localization offers a contextual synthetic lethality between combined EGFR and PARP inhibitors in triple negative breast cancer. The combination therapy induced persistent DNA double strand breaks responsible for enhanced cytotoxicity of TNBC to lapatinib and ABT-888, with >3-fold tumor growth delay in combination treatment vs. control.

2.3.2 Clinical Experience with Panitumumab

Monotherapy

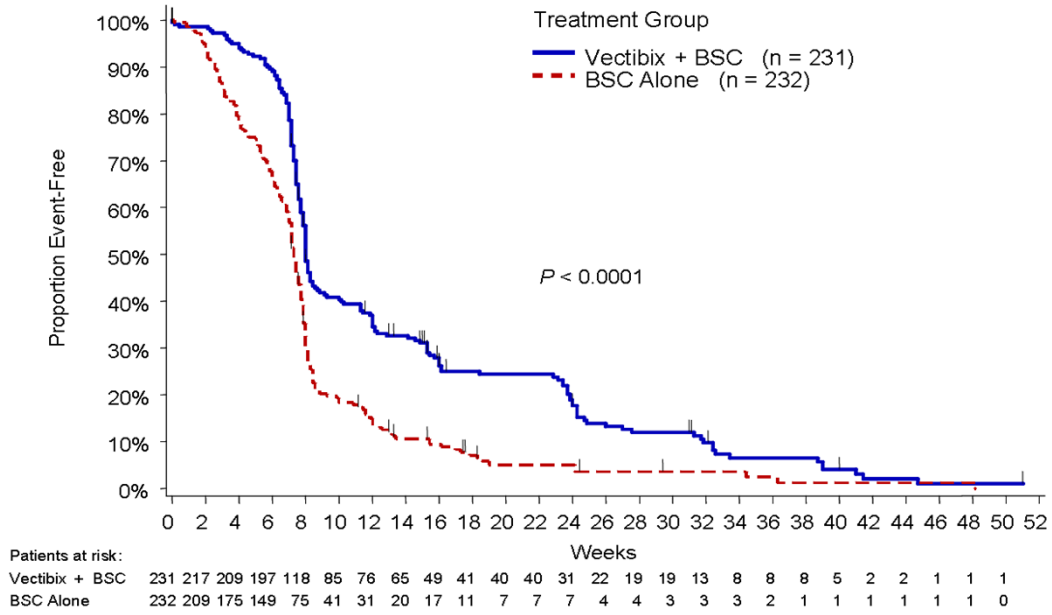
The safety and efficacy of Panitumumab were studied in Study 1, an open-label, multinational, randomized, controlled trial of 463 patients with EGFR-expressing, metastatic carcinoma of the colon or rectum (mCRC). Patients were required to have progressed on or following treatment with a regimen(s) containing a fluoropyrimidine, oxaliplatin, and irinotecan; progression was confirmed by an independent review committee (IRC) for 75% of the patients. All patients were required to have EGFR expression defined as at least 1+ membrane staining in ≥ 1% of tumor cells by the Dako EGFR pharmDx® test kit. Patients were randomized 1:1 to receive panitumumab at a dose of 6 mg/kg given once every 2 weeks plus best supportive care (BSC) (n = 231) or BSC alone (n = 232) until investigator-determined disease progression. Randomization was stratified based on ECOG performance status (0–1 vs 2) and geographic region (western Europe, eastern/central Europe, or other).

Upon investigator-determined disease progression, patients in the BSC-alone arm were eligible to receive panitumumab and were followed until disease progression was confirmed by the IRC. The analyses of progression-free survival (PFS), objective response, and response duration were based on events confirmed by the IRC that was masked to treatment assignment.

Based upon IRC determination of disease progression, a statistically significant prolongation in PFS was observed in patients receiving Panitumumab compared to those

receiving BSC alone. The mean PFS was 96 days in the Panitumumab arm and 60 days in the BSC-alone arm. Results are presented in Figure 1 below.

Figure 1. Kaplan-Meier Plot of Progression-Free Survival Time as Determined by the IRC



In a series of sensitivity analyses, including one adjusting for potential ascertainment bias, i.e., assessment for progressive disease at a nonstudy specified time point, PFS was still significantly prolonged among patients receiving panitumumab as compared to patients receiving BSC alone.

Of the 232 patients randomized to BSC alone, 75% of patients crossed over to receive panitumumab following investigator determination of disease progression; the median time to cross over was 8.4 weeks (0.3–26.4 weeks). Partial responses were identified by the IRC in 19 patients randomized to panitumumab, for an overall response of 8% (95% CI: 5.0%, 12.6%). No patient in the control arm had an objective response identified by the IRC. The median duration of response was 17 weeks (95% CI: 16 weeks, 25 weeks). There was no difference in overall survival between the study arms.

Panitumumab in Combination with Bevacizumab and Chemotherapy

Panitumumab shortened PFS, decreased survival time, and increased toxicity when given in combination with bevacizumab and chemotherapy in Study 2, a randomized, open-label, multicenter trial in the first-line treatment of metastatic colorectal cancer. Patients (n = 1053) were randomized 1:1 to panitumumab at a dose of 6 mg/kg given once every 2 weeks, in combination with bevacizumab and an oxaliplatin- or irinotecan-based 5-fluorouracil-containing chemotherapy regimen, or to bevacizumab and chemotherapy alone.

Randomization was stratified by type of regimen (oxaliplatin- or irinotecan-based); 86% of patients received an oxaliplatin-based regimen and 14% received an irinotecan-based regimen.
The major study objective was comparison of PFS in the oxaliplatin stratum as determined by an independent central review. An interim analysis based on 257 PFS events in the oxaliplatin stratum demonstrated shorter PFS in patients receiving Panitumumab, bevacizumab, and chemotherapy compared to those receiving bevacizumab and chemotherapy alone (median PFS were 8.8 months and 10.5 months; hazard ratio 1.44 [95% CI: 1.12, 1.85], p-value = 0.0024, Cox model with randomization factors as covariates). An unplanned analysis of overall survival after 155 deaths (both strata combined), conducted at the time of the interim analysis of PFS, yielded an adjusted hazard ratio of 1.55 [95% CI: 1.12, 2.14], comparing patients receiving Panitumumab, bevacizumab, and chemotherapy (92 deaths) to those receiving bevacizumab and chemotherapy alone (63 deaths)

Lack of Efficacy of Anti-EGFR Monoclonal Antibodies in Patients with mCRC Containing KRAS Mutations

Retrospective analyses across seven randomized clinical trials suggest that anti-EGFR-directed monoclonal antibodies are not effective for the treatment of patients with mCRC containing KRAS mutations. In these trials, patients received standard of care (i.e., BSC or chemotherapy) and were randomized to receive an anti-EGFR antibody (cetuximab or panitumumab) or no additional therapy. In all studies, investigational tests were used to detect KRAS mutations in codon 12 or 13. The percentage of study populations for which KRAS status was assessed ranged from 23% to 92%.

The data described in Table 2 and in other sections below, except where noted, reflect exposure to Panitumumab administered as a single agent at the recommended dose and schedule (6 mg/kg every 2 weeks) in 229 patients with mCRC enrolled in Study 1, a randomized, controlled trial. The median number of doses was five (range: one to 26 doses), and 71% of patients received eight or fewer doses. The population had a median age of 62 years (range: 27 to 82 years), 63% were male, and 99% were white with < 1% black, < 1% Hispanic, and 0% other.

Table 2. Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients with a Between-Group Difference of ≥ 5% (Study 1)

	Patients Treated With Vectibix Plus BSC (n = 229)		Best Supportive Care (BSC) Alone (n = 234)	
	Grade*			
Body System	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Body as a Whole				
Fatigue	26	4	15	3
General Deterioration	11	8	4	3
Digestive				
Abdominal Pain	25	7	17	5

Nausea	23	1	16	< 1
Diarrhea	21	2	11	0
Constipation	21	3	9	1
Vomiting	19	2	12	1
Stomatitis	7	0	1	0
Mucosal Inflammation	6	< 1	1	0
Metabolic/Nutritional				
Hypomagnesemia (Lab)	38	4	2	0
Peripheral Edema	12	1	6	< 1
Respiratory				
Cough	14	< 1	7	0
Skin/Appendages				
All Skin/Integument Toxicity	90	16	9	0
Skin	90	14	6	0
Erythema	65	5	1	0
Dermatitis Acneiform	57	7	1	0
Pruritus	57	2	2	0
Nail	29	2	0	0
Paronychia	25	2	0	0
Skin Exfoliation	25	2	0	0
Rash	22	1	1	0
Skin Fissures	20	1	< 1	0
Eye	15	< 1	2	0
Acne	13	1	0	0
Dry Skin	10	0	0	0
Other Nail Disorder	9	0	0	0
Hair	9	0	1	0
Growth of Eyelashes	6	0	0	0

[*] Version 2.0 of the NCI-CTC was used for grading toxicities. Skin toxicity was coded based on a modification of the NCI-CTCAE, version 3.0.

2.3.3 Rationale for Objectives

APC-induced blockage of base excision repair (BER) pathways have been shown to play a significant role in colorectal carcinogenesis, with implications for therapeutic targets. The product of the APC gene can modulate base excision repair (BER) pathway through an interaction with DNA polymerase β (Pol-β) and flap endonuclease 1 (Fen-1) to mediate CRC cell apoptosis. Since PARP inhibitors effectively block BER, PARP inhibition has the potential to increase the sensitivity of EGFR inhibition in both MMR-proficient and MMR-deficient colorectal tumors. Therefore, combining PARP and EGFR inhibition has the potential to confer synergistic benefit while also ameliorating a potential resistance mechanism to PARP inhibitor therapy. This combination has strong potential to offer a superior anticancer efficacy compared to each strategy alone.

2.3.4 Rationale for Measures

A safety run-in of the approved dose of Panitumumab safely combined with Niraparib will be done in the first 6 patients, given that there is no evidence or concerns of additive or overlapping toxicities between the two classes of agents being tested. An initial cohort of 6 RAS WT colorectal cancer (CRC) patients will be enrolled and treated for the safety run-in and will be monitored during cycle 1 for toxicities in excess of known side-effect profile of both agents. These 6 patients will also be evaluated for efficacy of the combination therapy.

Additional 20 CRC patients with the same inclusion criteria will be subsequently enrolled and treated to determine efficacy. Patients who fail screening will be replaced. We will consider the combination of Niraparib and Panitumumab to be ineffective if the true CBR is less than 10% (p0). We will also assume that the combination is worthy of further study if the true CBR rate is 25% or greater (p1). With an alpha of 0.1 and beta 0.8 (small pilot estimate of activity), the sample size will be 26 patients, enrolled and treated on this phase II study. Allowance will be made for patients who consent but fail screening for the clinical trial. Given our previous enrollment to colorectal cancer trials, we anticipate completion of enrollment in 18 months.

In addition, we plan to collect at study entry data on

a. Best response to prior therapy with Oxaliplatin (CR, PR, SD for more than 4 months OR Progression of Disease; PD)

b. Oxaliplatin refractory (progression on Oxaliplatin) OR sensitive (Oxaliplatin stopped due to neuropathy) disease.

We will evaluate the activity (CBR) of the regimen in in each group. This is a secondary hypothesis generating aim.

3 PARTICIPANT SELECTION

3.1 Inclusion Criteria

a. Participant must have advanced, metastatic RAS wildtype colorectal cancer and must have received at least one line of palliative systemic therapy. Both microsatellite (MSI-H) high and stable (MSS) patients are eligible

b. Participants may have been intolerant of, progressed on, or failed at least one line of systemic chemotherapy in the metastatic setting. Patients who are currently on first line Oxaliplatin-containing chemotherapy regimen are allowed on the trial if they have remained stable or better (PR or CR) for at least 4 months on that line of treatment and are being considered for maintenance therapy as standard of care.

c. Histologic or cytologic diagnosis of colorectal cancer

d. Participant must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.

e. Participant must be ≥ 18 years of age

f. Participant must have adequate organ function, defined as follows:

- Absolute neutrophil count ≥ 1,500/µL
- Platelets ≥ 100,000/µL
- Hemoglobin ≥ 9 g/dL
- Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation
- Total bilirubin ≤ 1.5 x ULN (≤2.0 in patients with known Gilberts syndrome) 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

g. Participant receiving corticosteroids may continue as long as their dose is stable for least 4 weeks prior to initiating protocol therapy.

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

i. Female participant has a negative urine or serum pregnancy test within 7 days prior to taking study treatment if of childbearing potential and agrees to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):

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

records of the actual procedure or confirmed by an ultrasound/screening CT/MRI scans. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. See Section 4.4 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

j. Participant must agree to not breastfeed during the study or for 180 days after the last dose of study treatment.

k. Male participant agrees to use an adequate method of contraception (see Section 4.4 for a list of acceptable birth control methods) starting with the first dose of study treatment through 180 days after the last dose of study treatment. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

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

3.2 Exclusion Criteria

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

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

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

d. Prior therapy with PARP inhibitors or with EGFR inhibitors approved for the treatment of colorectal cancer (Cetuximab or Panitumumab)

e. Patients with a history of interstitial pneumonitis or pulmonary fibrosis, or evidence of interstitial pneumonitis or pulmonary fibrosis during screening.

f. Inability to take oral medications.

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

h. Participant must not have a known hypersensitivity to components or excipients of Niraparib or Panitumumab.

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

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

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

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

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

n. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

o. Participant must not have had diagnosis, detection, or treatment of another type of cancer ≤ 2 years prior to initiating protocol therapy (except basal or squamous cell carcinoma of the skin and cervical cancer that has been definitively treated)

p. Participant must not have known active, symptomatic brain or leptomeningeal metastases. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging (CT/MRI) for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

4 TREATMENT PLAN

4.1 Method of Treatment Assignment

This is a non-randomized, phase II, open-label study.

4.2 Treatment Regimen

A. Panitumumab 6 mg/kg intravenous infusion on Day 1 and 15 of each 28-day cycle administered over 60 minutes (≤ 1000 mg) or 90 minutes (> 1000 mg).

B. Niraparib 200mg or 300mg (based on baseline weight and/or serum platelet count – see table 2 below) Oral, daily, continuously.

4.2.1 Niraparib Administration

Niraparib will be administered as a flat-fixed, continuous daily dose according to the Table 2 below. Niraparib should be swallowed whole and not opened, crushed or chewed. Food does not significantly affect the absorption of niraparib; therefore, niraparib may be taken without regard to meals. Participants should take doses at approximately the same times each day. Bedtime administration may be a potential method for managing nausea.

Vomited doses should not be made up.

If a participant misses a dose (greater than 12 hours from normal dosing time) of niraparib, they should skip that dose and take their next dose at its regularly scheduled time.

If niraparib is dose reduced, participants should be instructed to continue using their current supply at their new dose until their supply has been exhausted.

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

Table 2: Niraparib Dosing

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

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

4.2.2 Panitumumab Administration

Panitumumab is administered at 6 mg/kg intravenous infusion on Day 1 and 15 of each 28-day cycle, over 60 minutes (≤ 1000 mg) or 90 minutes (> 1000 mg). Pre-medications are allowed if the patient has received same for other monoclonal antibodies. Primary skin

prophylaxis must be instituted with initiation of therapy, including sunlight protection, skin care with hydrophilic cream, and oral antibiotics with doxycycline (100–200 mg/day for ≥8 weeks) or minocycline (100 mg/day for ≥8 weeks).

4.3 Prohibited Therapies

The following medications are prohibited while receiving protocol therapy:

- Systemic anticancer or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than niraparib
- Radiation therapy encompassing >20% of the bone marrow is prohibited within 2 weeks prior to Day 1 and during study treatment. Note: Palliative radiation therapy to a small field >1 week prior to Day 1 of study treatment may be allowed.
- Any surgery that involves tumor lesions. Note: Administration of radiation therapy or surgery done that involves tumor lesions will be considered as disease progression at the time the procedure is performed.
- Niraparib weakly induces Cytochrome P450 (CYP)1A2 in vitro and is a relatively poor substrate for P-glycoprotein (P-gp); therefore, investigators are advised to use caution with the substrates for CYP1A2 with a narrow therapeutic range, i.e. theophylline and tizanidine.
- Prophylactic cytokines (i.e., granulocyte colony-stimulating factor [GCSF]) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current American Society of Clinical Oncology (ASCO) guidelines.[30]

4.4 Birth Control

Participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation beginning with time of consent, during the study treatment and for 180 days after last dose of study treatment(s):

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral route
  - Intravaginal route
  - Transdermal route
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device

- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence, if the preferred and usual lifestyle of the subject

4.5 Breast Feeding

Participants must not breast-feed while receiving protocol therapy and for 180 days following the last dose of protocol therapy

4.6 Blood Donation

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

4.7 Treatment Discontinuation

Participants may continue protocol therapy until one of the following criteria applies:

- Disease progression
- Serious or life-threatening adverse event
- Severe noncompliance with protocol as judged by the Investigator and/or Sponsor
- Participant decision to withdraw
- Participant becomes pregnant
- Participant is diagnosed with MDS or AML (as confirmed by a hematologist)
- Investigator, Sponsor, and/or TESARO/GSK becomes aware of conditions or events that suggest a possible risk or hazard to participants if the clinical study continues

4.8 Duration of Follow Up

Participants will be followed for 5 years after removal from protocol therapy or until death, whichever occurs first.

4.9 Discontinuation from Study

Participants who discontinue from treatment will continue to be followed for overall survival until one of the following criteria apply:

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

For participants 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 participant before the participant is deemed lost to follow-up.

4.10 Participant Replacement Criteria

In the safety run-in cohort, patients who do not complete at least 75% of the intended course of chemotherapy due to reasons other than toxicity will be considered as in-evaluable for the primary endpoint and will be replaced.

5 DOSE MODIFICATIONS

5.1 Niraparib

Dose interruption and/or modification of niraparib may be implemented due to nonhematologic or hematologic toxicities per the Investigator's judgement after Cycle 1.

Treatment must be interrupted for any nonhematologic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib (Table 3). If the nonhematologic toxicity is appropriately resolved to baseline or Grade ≤1 within 4 weeks (28 days) of the dose interruption period, the patient may restart treatment with niraparib but with a dose level reduction if prophylaxis is not considered feasible (see Table 5). If the event recurs at similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made according to Table 3.

If the toxicity requiring dose interruption has not resolved completely or to CTCAE Grade 1 during the maximum 4-week (28-day) dose interruption period, and/or the patient has already undergone a dose reduction to a minimum dose of 100 mg QD, the patient must permanently discontinue treatment with niraparib.

The dose interruption and modification criteria for niraparib for hematologic parameters will be based on blood counts and are outlined in Table 8. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period, the patient must permanently discontinue treatment with niraparib.

For patients whose initial dose is 3 capsules daily (300 mg/day), dose reductions to 2 capsules daily (200 mg/day) and subsequently to 1 capsule daily (100 mg/day) will be allowed. No further dose reduction will be allowed.

For patients whose initial dose is 2 capsules (200 mg/day), dose reduction to 1 capsule once daily (100 mg/day) will be allowed. No further dose reduction will be allowed.

Both medications should be held at the same time.

Table 3: Recommended Dose Modifications for Adverse Reactions

A: Niraparib

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

Table 4: Niraparib Dose Modifications for Nonhematologic Adverse Reactions

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Table 5: Niraparib Dose Modifications for Hematologic Toxicity

Laboratory Abnormality	Intervention
Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time.	
Platelet count < 100,000/μL	First occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at same or reduced dose per Table 3. If platelet count is < 75,000/μL, resume niraparib at a reduced dose per Table 3.
	Second occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at a reduced dose per Table 3. Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil count < 1,000/μL	Withhold niraparib for a maximum of 28 days and monitor blood counts until neutrophil counts return to ≥1,500/μL. Resume niraparib at a reduced dose per Table3. Discontinue niraparib if neutrophil level has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone maximum dose reductions per Table 3.
Hemoglobin ≤ 8 g/dL	Withhold niraparib for a maximum of 28 days and monitor blood counts until hemoglobin returns to ≥9 g/dL. Resume niraparib at a reduced dose per Table 3. Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone maximum dose reductions per Table 3.

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

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

In the case of thrombocytopenia, following the first occurrence, resumption of therapy may occur at the same dose or 1 dose level lower when the hematologic toxicity has resolved. Subsequent occurrences should trigger dose reduction upon resumption of therapy. If the platelet count has not reverted within 28 days of interruption to ≥100,000/μL, then study treatment should be discontinued.

If dose interruption and/or modification is required at any point during study treatment because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until the AE resolves to the specified blood count levels. To ensure the safety of the new dose, weekly blood draws for CBC will be required for an additional 4 weeks after the AE has resolved, after which monitoring every 4 weeks may resume. CBC monitoring will continue every 4 weeks (ie, monthly) for the next 11 months of treatment, and periodically after this time.

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

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

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

B: Panitumumab

Dose level	
Starting dose	6mg/Kg body weight
First dose reduction	4mg/Kg body weight

The recommended dose of Panitumumab is 6 mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. Doses higher than 1000 mg should be administered over 90 minutes.

Appropriate medical resources for the treatment of severe infusion reactions should be available during Panitumumab infusions.

Dose Modifications for Infusion Reactions

Infusion reactions, manifesting as fever, chills, dyspnea, bronchospasm, and hypotension, can occur following Panitumumab administration.

- Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion.
- Immediately and permanently discontinue Panitumumab infusion in patients experiencing severe (grade 3 or 4) infusion reactions.

Dose Modifications for Dermatologic Toxicity

Primary skin prophylaxis must be instituted with initiation of therapy, including sunlight protection, skin care with hydrophilic cream, and oral antibiotics with doxycycline (100–200 mg/day for ≥8 weeks) or minocycline (100 mg/day for ≥8 weeks).

• Withhold Panitumumab for dermatologic toxicities that are grade 3 or higher or are considered intolerable. If toxicity does not improve to ≤ grade 2 within 1 month, permanently discontinue Panitumumab.

• If dermatologic toxicity improves to ≤ grade 2, and the patient is symptomatically improved after withholding no more than two doses of Panitumumab, treatment may be resumed at 67% of the original dose.

- If toxicities recur, permanently discontinue Panitumumab.
- If toxicities do not recur, subsequent doses of Panitumumab may be increased by increments of 25% of the original dose until the recommended dose of 6 mg/kg is reached.

Dose Modifications for Other Toxicities

- Electrolyte Depletion/Monitoring: Monitor patients for hypomagnesemia and hypocalcemia prior to initiating Panitumumab treatment, periodically during Panitumumab treatment, and for up to 8 weeks after the completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.
- Pulmonary Fibrosis/Interstitial Lung Disease (ILD): In the event of acute onset or worsening of pulmonary symptoms, interrupt Panitumumab therapy. Discontinue Panitumumab therapy if ILD is confirmed.
- Ocular Toxicities: Monitor for keratitis or ulcerative keratitis. Interrupt or discontinue Panitumumab for acute or worsening keratitis.

6 PHARMACEUTICAL INFORMATION

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.

6.1 Niraparib

6.1.1 Identity

Niraparib piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) -1 and -2 inhibitor. Niraparib is also known as ZEJULA.

6.1.2 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.

6.1.3 Packaging, Labeling and Storage

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

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

6.1.4 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 a patient identifier, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the pharmacy will be

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

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

6.1.5 Disposal and Destruction

Niraparib should be destroyed at the investigational site if permitted by local regulations.

6.2 Panitumumab

Panitumumab (Vectibix) is an epidermal growth factor receptor antagonist indicated as a single agent for the treatment of metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens. Approval is based on progression free survival; no data demonstrate an improvement in disease-related symptoms or increased survival with Panitumumab. Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Panitumumab in patients whose tumors had KRAS mutations in codon 12 or 13. Use of Panitumumab is not recommended for the treatment of colorectal cancer with these mutations.

6.2.1 Identity

Panitumumab is supplied as a sterile, colorless, preservative-free in a single-use vial. It is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Panitumumab has an approximate molecular weight of 147 kDa. Panitumumab is produced in genetically engineered mammalian (Chinese Hamster Ovary) cells.

Panitumumab is a sterile, colorless, pH 5.6 to 6.0 liquid for intravenous (IV) infusion, which may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates. Each single-use 5 mL vial contains 100 mg of panitumumab, 29 mg sodium chloride, 34 mg sodium acetate, and Water for Injection, USP. Each single-use 10 mL vial contains 200 mg of panitumumab, 58 mg sodium chloride, 68 mg sodium acetate, and Water for Injection, USP. Each single-use 20 mL vial contains 400 mg of panitumumab, 117 mg sodium chloride, 136 mg sodium acetate, and Water for Injection, USP.

6.2.2 Potential Risks of Panitumumab

Most common adverse reactions (≥ 20%) are skin toxicities (i.e., erythema, dermatitis acneiform, pruritus, exfoliation, rash, and fissures), paronychia, hypomagnesemia, fatigue, abdominal pain, nausea, diarrhea, and constipation.

6.2.3 Packaging, Labeling and Storage

Panitumumab (Vectibix) is provided as one vial per carton.

- Each 5 mL single-use vial contains 100 mg of panitumumab in 5 mL (20 mg/mL) (NDC 55513-954-01).
- Each 10 mL single-use vial contains 200 mg of panitumumab in 10 mL (20 mg/mL) (NDC 55513-955-01).
- Each 20 mL single-use vial contains 400 mg of panitumumab in 20 mL (20 mg/mL) (NDC 55513-956-01).

Store vials in the original carton under refrigeration at 2° to 8°C (36° to 46°F) until time of use. Protect from direct sunlight. DO NOT FREEZE. 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 storage and handling manual.

6.2.4 Disposal and Destruction

Since Panitumumab does not contain preservatives, any unused portion remaining in the vial must be discarded. The diluted infusion solution of Panitumumab should be used within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36° to 46°F). DO NOT FREEZE.

7 CORRELATIVE STUDIES

Biomarker analysis

Predictive biomarkers will be explored in RAS WT mCRC patients on this phase II study of Niraparib in combination with Panitumumab. Skin reactions to EGFRi have previously been showed to be surrogate markers for therapeutic efficacy. Skin punch biopsies are easily obtained in the clinic (compared to colorectal tumor tissue biopsies) and may be used for pharmacodynamic studies and to demonstrate early prediction of response to dual EGFR-PARP inhibition. Established and tailored statistical methods will be employed to distinguish the predictive impact of genetic abnormalities in both diagnostic tumor and research skin biopsies. Paired pre- and post-treatment skin biopsy samples will be used to determine changes to EGFR+PARP inhibition. Normal skin biopsies from regions that contained hair follicles will be obtained in the form of a 4-mm diameter punch biopsy (8 mm depth) before treatment and on day 22 of cycle 1.

Table X-1 Summary of Research Tissue and Blood Specimen Collection

Research Sampling	**Time point**	**Comments**
Skin Biopsy	Baseline, C1D22	4-mm diameter punch biopsy (8 mm depth) before treatment and on days 22 of cycle 1.
Archival Tissue	Screening	Tissue block/at least 10 FFPE slides availability for future correlative studies

7. A. Molecular profile of mCRC tumors:

Because outcomes are improved when novel therapies are applied, all patients who are newly diagnosed with mCRC are currently mandated by the professional society guidelines to be tested for mutations in KRAS, NRAS, and BRAF V600E, as well as for microsatellite instability–high (MSI-H) status or dMMR, HER2 amplifications and rare fusions such as NTRK. As standard of care (SOC) at Emory, patients with mCRC receive molecular profiling to evaluate for these therapeutic targets. Various commercial genomic platforms (e.g. CARIS, FoundationOne CDx™) are used in the clinical care of cancer patients at Emory. These next generation sequencing (NGS) based in-vitro diagnostic platforms are used for the detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in multiple genes and select gene rearrangements. In addition, genomic signatures are also detected on these platforms, including MMR/MSI and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. Genes tested include KRAS, NRAS, BRAF, HER2, NTRK, as well as DNA repair genes such as MLH1, MSH2, MSH3, PMS2, MSH6, BRCA1, BRCA2, ATM, ATR, PALB2, RAD51, BRIP1, PALB2, RAD51B, RAD51C, RAD51D, PARP1, PARP2, PARP3. PD-L1 statuses are also determined via immunohistochemistry (IHC) using Dako 22C3 or Ventana SP142 antibodies. DDR gene deficiencies can lead to dysfunctional DNA

repair or chromosome instability, altering features of the somatic genome. To identify the association between DDR deficiency and response to the investigational combination therapy, a multivariate regression model corrected for clinical variables such as demographics and duration of response to frontline platinum chemotherapy will be utilized. Tumors of HRD alteration carriers are known to exhibit distinct somatic mutational signatures reflecting their specific damages. DDR-associated somatic mutational signatures will be identified using the same multivariate regression model.

7. B. Impact of dual EGFR-PARP inhibition on cytotoxic markers and infiltrating immune cells in skin biopsies.

Collected pre- and on-treatment skin biopsies will be analyzed for the following biologic properties and correlated with clinical outcomes:

1. Four metrics of cytotoxicity – Caspace-3, γ-H2AX, PARP, MAPK, together with indicators of EGFR downregulation.
2. Tumor infiltrating cells using multiplex immunofluorescence panels.

7.1 Pharmacokinetics

N/A

8 SCHEDULE OF ASSESSMENTS

8.1 Screening

At Screening, the following procedures/tests will be performed:

- Informed Consent
- ECOG Performance Status
- Physical Exam
- Medical History and Concomitant Medications
- Vital Signs: systolic and diastolic blood pressures, weight and temperature
- Height
- Pregnancy testing within 7 days prior to initiating protocol therapy
- CBC with differentials
- Comprehensive metabolic panel
- Urinalysis

8.2 Cycle 1

On Days 1 and 15, the following procedures/tests will be performed:

- Vital signs: systolic and diastolic blood pressures, weight, and temperature
- CBC
- Comprehensive metabolic panel
- Urinalysis
- Adverse event monitoring

On Day 8 CBCs will be performed.

On Day 22, Skin biopsy and CBCs will be performed.

8.3 Subsequent Cycles

On Days 1 and 15, the following procedures/tests will be performed:

- Vital signs: systolic and diastolic blood pressures, weight, and temperature
- CBC with differentials
- Comprehensive metabolic panel

- Urine pregnancy test for females of childbearing potential conducted every 3 cycles for duration of study (ie, Cycle 4, Cycle 7, etc.).
- Urinalysis
- Adverse event monitoring

8.4 End of Treatment

- Adverse event monitoring

8.5 Safety Follow-up

Follow-up visit should occur at least 30 days from the last administered dose of protocol therapy.

- Vital signs: systolic and diastolic blood pressures, weight, and temperature
- CBC
- Comprehensive metabolic panel
- Urine pregnancy test for females of childbearing potential
- Coagulation
- Urinalysis
- Physical Exam
- Adverse event monitoring
- Assess for MDS/AML

8.6 Long Term Follow-up

- Survival assessment
- Follow-up for MDS/AML

8.7 Unscheduled Assessments

- 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 Institution and TESARO/GSK within 24 hours of becoming aware of the SAE
- Clinical Laboratory Assessments

- 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
- For any suspected MDS/AML case reported while a participant is receiving treatment or being 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. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization criteria) and other sample testing reports related to MDS/AML. The site must keep a copy of the report with the participant's study file.

9 STUDY CALENDAR

Screening assessments are to be conducted within 28 days prior to initiating protocol therapy unless otherwise specified. Screening assessments occurring within 1 week prior to initiating study treatment do not need to be repeated on Cycle 1 Day 1 unless otherwise specified.

Screening laboratory assessments must be done within 8 days prior to initiating protocol therapy. For women of childbearing potential, as defined in the eligibility criteria, a pregnancy test must be completed within 7 days prior to initiating protocol therapy. If a urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Study Procedures	**Screening (-28 to -1 days)**	**Cycle 1**				**Cycle 2**		**Cycle 3+**		**EOT**	**Safety Follow-Up**	**Long Term Follow-Up**
		D1	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**D15**		**At least 30 days from last dose**	**Every 6 months for 2 years and annually thereafter[g]**
Written informed consent	X											
Inclusion/Exclusion Criteria	X											
Height	X											
Vital signs and weight [a]	X	X		X		X	X	X	X		X	
ECOG Performance Status	X	X		X		X	X	X	X			
Medical History [b]	X	X		X		X	X	X	X		X	
Results of prior genomic profiling (including extended RAS analysis)	X											
Concurrent Medications	X	X		X		X	X	X	X			
Physical Exam	X	X		X		X	X	X	X		X	
Adverse Event Monitoring		X				X		X		X	X	
Assess for MDS/AML		X				X		X		X	X	X
Pregnancy Testing [c]	X							X[c]			X	
PT/INR and aPTT	X											
CBC with differential [d]	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Metabolic Panel [e]	X	X				X		X		X	X	
Urinalysis	X	X				X		X		X	X	
Skin biopsy for correlative studies[f]	X				X							
Panitumumab Administration		X		X		X	X	X	X			
Niraparib dispensed		X				X		X				
Pill Diary and pill count				X		X	X	X	X			
Bone marrow aspirate and biopsy [h]	X											
Survival assessment [h]												X[g]
Tumor Assessment/Imaging (CT/MRI)	X[i]						X[j]					
Archival Tissue	X											

Study Procedures	Screening (-28 to -1 days)	Cycle 1				Cycle 2		Cycle 3+		EOT	Safety Follow-Up	Long Term Follow-Up
		D1	D8	D15	D22	D1	D15	D1	D15		At least 30 days from last dose	Every 6 months for 2 years and annually thereafter[g]
	Panitumumab: 6 mg/kg intravenous infusion on Days 1 and 15 of each 28-day cycle administered over 60 minutes (≤ 1000 mg) or 90 minutes (> 1000 mg). Niraparib: 200mg or 300mg (based on baseline weight or serum platelet count) Oral, daily, continuously. a. Vital signs to include: systolic and diastolic blood pressures while the patient is in a seated position, weight, and temperature b. Medical History should include all prior anticancer therapy c. Female subjects of childbearing potential as defined in the eligibility criteria must have a serum or urine beta-hCG pregnancy test within ≤ 7 days prior to initiating protocol therapy, every 3 cycles (i.e. C4D1, C7D1) and at End of Treatment d. CBC to include absolute neutrophil count, platelets, and hemoglobin. CBC must be collected on Cycle 1 Day 1. e. Comprehensive metabolic panel to include: serum creatinine, total bilirubin, aspartate aminotransferase and alanine aminotransferase. f. Normal skin biopsies from regions containing hair follicles will be obtained in the form of a 4mm diameter punch biopsy (8 mm depth) before treatment and on days 22 of cycle 1. The biopsies will be evaluated for expression of p-Caspace-3, PARP, p-MAPK, Ki-67, and p27 by IHC. g. Overall survival to be followed for 5 years following the last dose of Niraparib. h. For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to TESARO/GSK. A copy of the hematologist's report of aspirate/biopsy findings including a classification according to WHO criteria and other sample testing results related to MDS/AML will be provided to the PI and to TESARO/GSK. i. Baseline imaging within 4 weeks of day 1 is mandatory. CT or MRI acceptable j. Restaging scans prior to odd treatment cycles											

10 ADVERSE EVENT REPORTING

10.0 Definition of Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

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

10.1 Serious Adverse Events (SAEs)

Any untoward medical occurrence that, at any dose;

- Results in death;
- Is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization* or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event**

*Exception: Preplanned (at time of informed consent) hospitalization for elective procedures, for protocol compliance or social reasons, or for observation will not be considered criteria for an SAE. The reason for the planned hospitalization should be documented. Complications experienced during these hospitalizations must be reported as SAEs if hospitalization is prolonged due to AE, or if the complication meets other serious criteria).

**Medical and scientific judgment should be exercised in determining whether situations or events should be considered serious adverse events: an important medical event may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the study drug.

10.2 Adverse Event 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 TESARO/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
- Embyro-fetal toxicity

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

- MDS and AML along with other secondary cancers should be reported to the Sponsor Institution and to TESARO/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 Institution and to TESARO/GSK through 90 days after the last dose of niraparib.
- Embryo-fetal toxicity should be reported as outlined in the Pregnancy reporting section.

10.3 Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure

- **Abuse:** is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.
- **Misuse:** medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Medication error:** is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** is a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. If an overdose with a TESARO/GSK product, the Sponsor Institution and TESARO/GSK should be notified immediately, and the patient should be observed closely for Aes. Associated Aes should be treated and monitored by the Investigator. The dosage of study drug administered, any associated Aes,

and/or treatment provided to the patient because of the overdose, should be reported.

- **Accidental /Occupational exposure:** is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure associated with a TESARO/GSK product must be reported on a Special Situations Report Form to the Sponsor Institution and to TESARO/GSK within 5 business days of awareness regardless of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an AE, an SAE Report Form must also be submitted to the Sponsor Institution and to TESARO/GSK within 24 hours of awareness.

10.4 Assessment of Adverse Events

Each AE will be assessed by the investigator for severity and for a causal relationship with the study treatment as outlined below.

10.4.1 Severity Assessment

All Aes will be assessed by the Investigator for severity according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03: 14 June 2010; National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity grades 1 through 5 provide unique clinical descriptions of severity of each adverse event. The CTCAE v4.03 is available on the NCI/NIH website.

Please note that there is a distinction between **serious** and **severe** Aes: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.1. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

10.4.2 Relationship to Study Drug

The Investigator must provide a causality assessment regarding the relationship of the event with the study drug for all Aes. One of the following categories should be selected based on medical judgment, considering all contributing factors:

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

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

10.5 Collection and Recording of Adverse Events

Aes may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as, “How have you been feeling since your last study visit?” The Investigator will document the nature of AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

Aes, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All SAEs will be collected from the administration of the first dose of study drug and must be throughout the study and for at least 30days after the last dose of protocol therapy.

SAEs considered by the Investigator to be related to study medication will be reported regardless of the timeframe from last dose of protocol therapy.

All Aes will be documented for each patient from the administration of the first dose of study drug and must be throughout the study and for at least 30days after the last dose of protocol therapy.

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

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

10.6 Follow-Up of Adverse Events

All Aes experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

10.7 Reporting to the Sponsor Institution

All SAEs and AESIs must be reported to the Sponsor Institution within 24 hours of becoming aware of the initial SAE/AESI or any follow-up information regarding the SAE/AESI using the SAE reporting information below. SAEs/AESIs must be reported after study completion if the SAE/AESI is assessed as study-drug related.

MedWatch 3500 Reporting Guidelines:

Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to TESARO/GSK at the time of submission to FDA.

10.8 Reporting to TESARO/GSK

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

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

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

TESARO/GSK SAE, Pregnancy, and AESI Reporting Information
Email: OAX37649@gsk.com Fax: +44(0) 208754 7822

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

10.9 Quarterly AE/SAE Reporting to TESARO/GSK

On a quarterly basis the Sponsor Institution will provide TESARO/GSK with a line listing of all adverse events (serious and non-serious) received during a defined

quarter. The line listing will include a subject ID, the AE term, onset date, outcome, causality assessment, severity, and study drug dosing information.

10.10 Pregnancy

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

The Sponsor Institution must report all pregnancies associated with TESARO/GSK product including follow up outcomes to TESARO/GSK within 1 business day 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 TESARO/GSK within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

10.11 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. Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

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 TESARO/GSK per the governing institutional requirements and in compliance with local laws and guidelines.

10.12 Reporting Product Complaints for Niraparib

Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the Sponsor Institution or qualified designee to GSK within 1 working day of first becoming aware of the possible defect to GSK QA at gsk-rd.complaints@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.

11 DATA REPORTING

11.0 Data and Safety Monitoring

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed Moderate Risk (such as the current protocol as per Emory standards), initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, Aes/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Decisions regarding moving forward from the safety run-in cohort to the expansion phase will be discussed at the GI working group. The PI or designee must obtain approval from the DSMC for expansion. A copy of the DSMC approval letter will be forwarded to TESARO/GSK. A copy of the de-identified DSMC may be requested by TESARO/GSK, but approval of such requests are subject to DSMC internal policies.

PI and the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet to review and discuss study data to ensure subject safety. During the meetings, the PI or co-I will review the eligibility criteria for each new patient. In addition, during these meeting the group will review all the toxicity (AE/SAE) logs, random checks of case report form completion and roadmap for each patient on the trial. All study personnel will be trained on the protocol by the PI or co-I. Study personnel will sign training log prior to being included on delegation of authority log. All AE and SAE will be handled according to Section 10 which provides detailed instructions on reporting requirements.

12 STATISTICAL METHODS

12.1 Study Design and Endpoints

- PFS, defined as the time from the date of the start of study treatment to the earlier date of assessment of progression or death by any cause in the absence of progression. Progression will be assessed by RECIST v.1.1 criteria using an independent review.
- ORR, defined as the percentage of patients with CR or PR, as assessed by RECIST v.1.1 criteria using an independent review.
- DOR, defined as the time from the initial response (CR or PR) until the time of first documentation of disease progression, as assessed by RECIST v.1.1 criteria using an independent review.
- DCR, defined as the percentage of patients with CR, PR or SD, as assessed by RECIST v.1.1 criteria using an independent review.
- OS, defined as measured from the date of randomization (or from the start of study treatment if it is a non-randomized study) to the date of death by any cause
- Safety endpoints include the incidence of treatment-emergent AEs (TEAEs), changes in clinical laboratory parameters (hematology, chemistry), vital signs, physical examinations, and usage of concomitant medications.

12.1.1 Primary Endpoint

The primary endpoint is clinical benefit rate (CBR) = Complete Response + Partial Response + Stable disease (CR +PR + SD) rate. In addition to the 6 patients enrolled a**nd treated** in the safety run-in cohort, 20 CRC patients with the same inclusion criteria will be subsequently enrolled and treated to determine efficacy.

12.1.2 Secondary Endpoints

A. Toxicity profile of the combination of Panitumumab and Niraparib; additional patients enrolled and treated on the expansion cohort to confirm the toxicity profile.

B. Efficacy endpoints: Objective response rate, response duration, overall survival and progression free survival. This will only be preliminary data since this is a secondary objective.

C. Biomarker analysis: The objective of the correlative assays is to identify patients who are more likely to respond to the combination. As a standard of care at Emory, patients with stage IV CRC receive genomic profiling to evaluate for therapeutic targets. We propose analyzing these profiles to identify patients with defects in their DNA repair pathways as a potential

biomarker for this regimen. Normal skin biopsies from regions that contained hair follicles will be obtained in the form of a 4-mm diameter punch biopsy (8 mm depth) before treatment and on days 22 of cycle 1. The biopsies will be evaluated for expression of p-Caspace-3, PARP, p-MAPK, Ki-67, and p27 by IHC.

12.1.3 Sample size, Accrual Rate and Study Duration

The sample size of this Phase II study is driven by the primary endpoint of CBR. We will consider the combination of Niraparib and Panitumumab to be ineffective if the true CBR is less than 10% under the null hypothesis. We will also assume that the combination is worthy of further study if the true CBR rate is 25% or greater under alternative hypothesis. With an alpha of 0.1 and using a one-sided Z test that uses S(P0) to estimate the standard deviation, the sample size will be 26 enrolled and treated patients for this study in order to achieve at least 80% power to detect the improvement. Patients who fail screening will be replaced. Given our previous enrollment to colorectal cancer trials, we anticipate completion of enrollment in 18 months.

12.1.4 Interim Monitoring Plan

No interim analysis is planned.

12.1.5 Analysis of Primary Endpoints

The efficacy, as measured by CBR, will be assessed for the total number of patients enrolled and treated. The rates of CBR will be presented as a point estimate with a 95% exact binomial confidence interval. Assuming 6 patients were enrolled and treated in the safety run-in cohort and an additional 20 patients for the cohort expansion, the 95% exact binomial confidence interval for the CBR rate will be within +/- 20%. Chi-square test or Fisher's exact test will be used to compare the efficacy in term of CBR between the different groups stratified by dose level or other factors, respectively. Logistics regression model will be further employed to test the adjusted effect of dosage on the CBR rate after adjusting for other clinical factors and demographic factors.

12.1.6 Analysis of Secondary Endpoints

Objective response rate will be calculated as proportion (Responders/Total patients) along with 95% confidence intervals using the Clopper-Pearson method. Chi-square test or Fisher's exact test will be used to compare the efficacy in term of response rate between the different groups stratified by dose level or other factors, respectively. Logistics regression model will be further

employed to test the adjusted effect of dosage on the response rate after adjusting for other clinical factors and demographic factors.

Response duration will be summarized as mean and standard deviation or median with range. Two sample t-test or General Linear Model (GLM) will be used to compare the response duration between different groups stratified by different factors, respectively.

For progression free survival, progression or death from any cause will be defined as the event. Patients will be censored at time of last follow-up. For overall survival, death from any cause will be defined as the event. Patients will be censored at time of last follow-up. Overall survival (OS) and progression free survival (PFS) rates of two patient groups stratified by dose levels or other factors will be estimated with the Kaplan-Meier method and compared between different groups using the log-rank test, respectively. The PFS and OS of each patient group at specific time points, such as 6 months, 1 year, 3 year, and 5 year, etc. will also be estimated alone with 95% CI. Cox proportional hazards models will be further used in the multivariable analyses to assess adjusted effect of the treatment regimen on the patients' OS and PFS after adjusting for other factors. Interaction terms between these factors will also be tested for statistical significance. The proportional hazards assumption will be evaluated graphically and analytically with regression diagnostics. Violations of the proportional hazards assumptions will be addressed by use of time-dependent covariates or extended Cox regression models.

For the biomarker study, descriptive statistics will be first used to summarize biomarker endpoints, including analyses of tumor biopsies. Biomarker data will also be displayed graphically, where appropriate. Depending on whether data is normally distributed, t-test or Wilcoxon rank sum test will be used to compare each biomarker between any two groups stratified by dosage, response, or other factors, respectively. General linear model (GLM) will be used to compare each biomarker between multiple dose levels with and without adjusting for other factors. Logistics regression model will be further employed to test the adjusted effect of biomarker on the response rate after adjusting for dosage as well as other factors.

12.2 Safety Analyses

Adverse event terms will be coded using the current version of the Medical Dictionary and will be summarized for all treated participants. Incidence of AEs occurring during the study will be summarized by system organ class and preferred term. Adverse events will also be summarized by causality and grade. Serious adverse events will be listed separately. Descriptive summary statistics will be used to summarize changes over time in laboratory values, vital signs, and physical examination findings

for all treated participants. Laboratory parameter changes will be described using shift tables, relative to CTCAE.

Scheduled times of the safety evaluations, rather than actual times, will be used in the summaries of safety data. No inferential hypothesis testing will be performed on the safety variables. Repeated or unscheduled results will not be included in the summaries but will be listed. All the important deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be described.

13 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

13.0 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the FDA Guidance and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study. All potential serious breaches must be reported to the Study Sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study. Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

13.1 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. In situations where consent cannot be given by subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate. The informed consent form (ICF) for this study will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1. Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.

2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

4. Obtain the IRB/IEC’s written approval/favorable opinion of the written ICF(s) and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The subject must be informed about the nature of the study to the extent compatible with his or her understanding, and he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator. The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

13.2 Protocol Approval and Amendment

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to subjects and any updates. The investigator should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- TESARO/GSK
- Regulatory Authority(ies), if required by local regulations

13.3 Investigator Responsibilities

By signing the Form FDA 1572, the Investigator agrees to conduct the study according to the protocol and the FDA regulations set forth in 21 CFR Parts 50, 54, 56, and 312.

The Investigator must provide TESARO/GSK with the following documents prior to the enrollment of any subjects:

- Copy of the IRB/IEC approval letter for protocol, informed consent, Investigator and site
- Valid medical license and Signed and dated current curricula vitae of the investigator
- Copy of approved informed consent document
- Copy of the FDA letter and IND receipt and number assignment
- Signed Clinical Trial Agreement

Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

13.4 Subject Confidentiality and Data Protection

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization. The consent form(s) must also include a statement that the study Sponsor and regulatory authorities have direct access to subject records, and that TESARO/GSK may also access records if applicable.

13.5 Access to Source Documents

If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, AE tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

13.6 Archival

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

13.7 Publications

The data collected during this study are confidential and proprietary to the study sponsor. Any publications or abstracts arising from this study will be discussed with TESARO/GSK prior to publication or presentation. Draft publications, including abstracts or detailed summaries of any proposed presentations will be submitted to TESARO/GSK at the earliest practicable time for review.

14 REFERENCES

1. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med.* 2009;361(2):123-134.
2. De Lorenzo SB, Patel AG, Hurley RM, Kaufmann SH. The Elephant and the Blind Men: Making Sense of PARP Inhibitors in Homologous Recombination Deficient Tumor Cells. *Front Oncol.* 2013;3:228.
3. Jones P, Wilcoxen K, Rowley M, Toniatti C. Niraparib: A Poly(ADP-ribose) Polymerase (PARP) Inhibitor for the Treatment of Tumors with Defective Homologous Recombination. *J Med Chem.* 2015;58(8):3302-3314.
4. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol.* 2011;12(9):852-861.
5. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. *Nat Rev Cancer.* 2004;4(10):814-819.
6. Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011;474(7353):609-615.
7. Timms KM, Abkevich V, Hughes E, et al. Association of BRCA1/2 defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. *Breast Cancer Res.* 2014;16(6):475.
8. Turner NC, Ashworth A. Biomarkers of PARP inhibitor sensitivity. *Breast Cancer Res Treat.* 2011;127(1):283-286.
9. Kummar S, Ji J, Morgan R, et al. A Phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *Clin Cancer Res.* 2012;18(6):1726-1734.
10. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med.* 2012;366(15):1382-1392.
11. Sandhu SK, Schelman WR, Wilding G, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a Phase 1 dose-escalation trial. *Lancet Oncol.* 2013;14(9):882-892.
12. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet.* 2010;376(9737):235-244.
13. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *The New England journal of medicine.* 2016;375(22):2154-2164.
14. Pujade-Lauraine E, Ledermann JA, Penson RT, et al. Treatment with olaparib monotherapy in the maintenance setting significantly improves progression-free survival in patients with platinum-sensitive relapsed ovarian cancer: Results from the phase III SOLO2 study. 48th Annual Meeting for the Society of Gynecologic Onocolgy. March 12-15, 2017. National Harbor, Maryland. Abstract# LBA-2.

15. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med.* 2017.
16. Data on file.
17. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA: a cancer journal for clinicians.* 2018;68(1):7-30.
18. Wu M, Rivkin A, Pham T. Panitumumab: human monoclonal antibody against epidermal growth factor receptors for the treatment of metastatic colorectal cancer. *Clin Ther.* 2008;30(1):14-30.
19. Rowinsky EK, Schwartz GH, Gollob JA, et al. Safety, pharmacokinetics, and activity of ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with metastatic renal cell cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2004;22(15):3003-3015.
20. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(13):1658-1664.
21. Hecht JR, Patnaik A, Berlin J, et al. Panitumumab monotherapy in patients with previously treated metastatic colorectal cancer. *Cancer.* 2007;110(5):980-988.
22. Berlin J, Posey J, Tchekmedyian S, et al. Panitumumab with irinotecan/leucovorin/5-fluorouracil for first-line treatment of metastatic colorectal cancer. *Clin Colorectal Cancer.* 2007;6(6):427-432.
23. Sobrero A, Lonardi S, Rosati G, et al. FOLFOX or CAPOX in Stage II to III Colon Cancer: Efficacy Results of the Italian Three or Six Colon Adjuvant Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2018;36(15):1478-1485.
24. Ciardiello F, Normanno N, Martinelli E, et al. Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): a randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX. *Ann Oncol.* 2016;27(6):1055-1061.
25. Colucci G, Giuliani F, Garufi C, et al. Cetuximab plus FOLFOX-4 in untreated patients with advanced colorectal cancer: a Gruppo Oncologico dell'Italia Meridionale Multicenter phase II study. *Oncology.* 2010;79(5-6):415-422.
26. Rothenberg ML, Cox JV, Butts C, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. *Ann Oncol.* 2008;19(10):1720-1726.
27. Aggarwal N, Donald ND, Malik S, Selvendran SS, McPhail MJ, Monahan KJ. The Association of Low-Penetrance Variants in DNA Repair Genes with Colorectal Cancer: A Systematic Review and Meta-Analysis. *Clin Transl Gastroenterol.* 2017;8(7):e109.
28. Edwards SL, Brough R, Lord CJ, et al. Resistance to therapy caused by intragenic deletion in BRCA2. *Nature.* 2008;451(7182):1111-1115.

29. Sakai W, Swisher EM, Jacquemont C, et al. Functional restoration of BRCA2 protein by secondary BRCA2 mutations in BRCA2-mutated ovarian carcinoma. *Cancer Res.* 2009;69(16):6381-6386.
30. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol.* 2006;24(19):3187-3205.
31. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.

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

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.
**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960:11:7-33.

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

APPENDIX 2 – RESPONSE CRITERIA

Response will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors using an independent review.

RECIST version 1.1* will be used in this study for assessment of tumor response [31]. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX 3 – DRUG DIARY

Protocol	Subject Number	Subject Initials	Visit
WCI ☐☐☐☐	☐☐☐☐☐☐☐☐	☐☐☐	**Cycle** ☐

Patient Diary

Please use this diary to record your daily protocol medication.

Use the back of the form to make notes about symptoms you experience, and for other medicine you have taken, and anything else you think would be of interest.

Dose of Niraparib _____ mg PO daily

Week 1 **Date** **Time Taken**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 2 **Date** **Time Taken**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 3 **Date** **Time Taken**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 4 **Date** **Time Taken**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**

Please sign at the completion of this cycle and **return with pill bottle** to the study team.

Patient's Signature _____ Date_____

Health/Medical Complaints

Please record all health/medical complaints you may have experienced below.

Please describe what you experienced	Date Started	Date Stopped

Other Medications

Record all medications taken during this cycle for example prescriptions and over the counter including vitamins.

Name of medication	Why did you take the medication?	Date Medication Started	Date Medication Stopped

If you have any questions, please call: 404 778 1900 or _____