Phase I/II Study of Niraparib with Radiotherapy for Treatment of Metastatic Invasive Carcinoma of the Cervix (NIVIX)

Sponsor:	Baylor College of Medicine
Principal Investigator:	Michelle S. Ludwig, MD, MPH, PhD
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The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements including but not limited to Institutional Review Board/Ethics Committee (IRB/EC) approval.

Confidentiality Statement

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Declaration of Sponsor or Responsible Medical Officer

Title: Phase I/II Study of Niraparib with Radiotherapy for Treatment of Metastatic Invasive Carcinoma of the Cervix (NIVIX)
Version Date: December 4, 2019

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.

Sponsor

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Declaration of the Investigator

Title: Phase I/II Study of Niraparib with Radiotherapy for Treatment of Metastatic Invasive Carcinoma of the Cervix (NIVIX)
Version Date: December 4, 2019

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

Investigator

_____ _____

[Michelle S. Ludwig] **Date**
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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event 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
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DDR	DNA damage repair
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
FE	food effect
gBRCA	germline breast cancer gene
GCSF	Granulocyte-colony stimulating factor
GBM	glioblastoma multiforme
hCG	human chorionic gonadotropin
HDR	High Dose Rate (brachytherapy)
HR	homologous recombination
HRD	homologous recombination deficiency
ICRU	International Commission on Radiation Units
irAEIs	immune-related adverse events of interest
IUD	intrauterine device
LDR	Low Dose Rate (brachytherapy)
LLN	Lower limit of normal
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

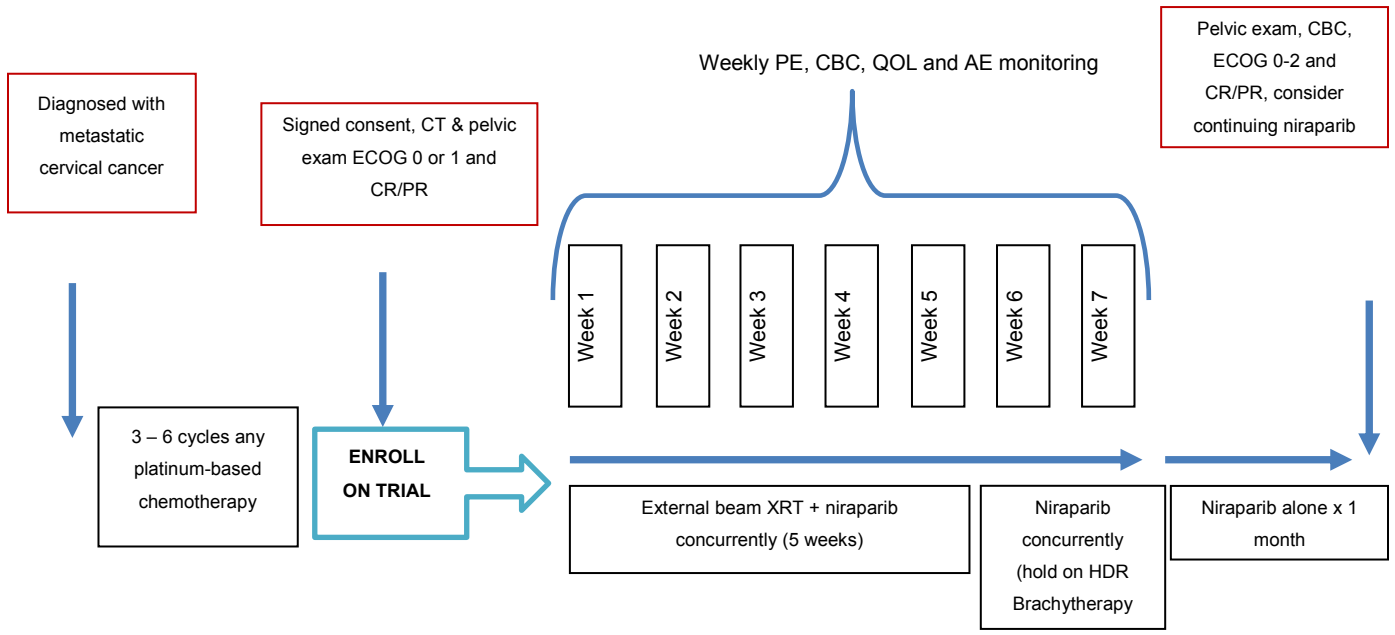
Abbreviation	Definition
NHEJ	non-homologous end joining
PARP	poly(ADP-ribose) polymerase
PFS	progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PRO	patient reported outcomes
PS	performance status
QD	once a day
QTc	corrected QT interval
SAE	serious adverse event
TEAES	treatment-emergent adverse events
ULN	upper limit of normal

1 INTRODUCTION

1.1 Study Design

This study will be conducted using a Bayesian Optimal Interval (BOIN) design with a target rate of dose limiting toxicities (DLT) set at 0.3. The BOIN design chooses the dose of study drug utilized for new patients based on the already observed incidence of toxicities. If the toxicity rate at the current dose is low, dose will be increased, whereas, the dose will be de-escalated if the observed toxicity rate is high. Additional patients will be treated as long as the observed toxicity rate remains indeterminate. For the purposes of this study, two dose levels of niraparib (100mg and 200 mg) will be evaluated concomitant with the concurrent administration of pelvic radiotherapy. Enrollment continues until 17 patients are enrolled at a safe dose for efficacy evaluation. A treatment scheme that outlines use of both pelvic radiotherapy and niraparib is found in Fig. 1. Study drug will be initiated at a dose of 100mg and escalate / de-escalate according to criteria specified in Table 2. This combination Phase I/II design ensures enrollment of the required number of patients for efficacy endpoint, while continuously monitoring safety, ensuring correct selection of the maximum tolerated dose (MTD) and allocation of maximum number of patients to the MTD group.

Figure 1:



1.2 Primary Objective

A. To establish the maximum tolerated dose (MTD) of niraparib when administered concurrently with whole pelvic radiotherapy.

B. Determine the local (pelvic) control for patients with metastatic cervical cancer treated with definitive pelvic radiotherapy.

1.3 Secondary Objectives

A. Assess the acute toxicity profile of niraparib administered concurrently with whole pelvic radiotherapy.

B. Assess quality of life for women receiving niraparib concurrently with whole pelvic radiotherapy.

C. Assess tumor response outside the radiation field for women receiving niraparib concurrently with whole pelvic radiotherapy.

1.4 Correlative Objectives

Pharmacodynamics (PARP Testing and percent inhibition by niraparib)

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 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. It was granted fast track designation by the FDA and approved on March 27, 2017 in the US for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum based chemotherapy.

2.2.1 Non-clinical 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

2.2.2.1 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.

2.2.2.2 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.[60]

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.

2.2.2.3 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. 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 progression-free survival (PFS). A total of 203 patients were enrolled 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 tumors were identified as homologous recombination deficiency positive (HRDpos), and 134 had tumors that were HRD negative (HRDneg). HRD status was assessed as indeterminate 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 (i.e., 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 (i.e. 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 (i.e. plasma concentration) of niraparib and QTc changes (i.e. change in corrected QT interval calculated using Fridericia's formula [ΔQTcF]).

2.3 Rationale for Current Study

Invasive carcinoma of the uterine cervix is the fourth most common cancer diagnosed in women worldwide. Each year, more than 528,000 women are newly diagnosed with an invasive cervical cancer. More than 266,000 deaths occur annually as a result of this disease[1]. Regions with the highest incidence are located in parts of Africa, Latin America and the Caribbean that lack population-based screening programs. Collectively, nearly 84% of invasive carcinomas of the cervix are diagnosed in less developed parts of the world where screening is not readily available. In the United States, there are 13,000 new cases and 7,000 deaths due to an invasive carcinoma of the cervix annually. Unfortunately, the burden of cervical cancer disproportionately impacts disadvantaged communities where routine access to screening is often limited.[2]

Patients with early-stage disease are curable with surgery and/or chemoradiation. About 50% of women in the United States presenting with cervical cancer will present with localized disease requiring chemoradiation[3]. Platinum-based chemotherapy is considered the gold standard for concurrent chemosensitization[4-7]. In a recent meta-analysis, the addition of sensitizing chemotherapy improved the 5 year overall survival rate by 6% (HR 0.81: 60 vs 66%). Two year progression-free survival is approximately 80% for women who concurrently receive sensitizing doses of cisplatin, but only 70% for those who do not.[8] However, the addition of cisplatin-based chemotherapy increases the incidence of acute hematological and gastrointestinal toxicities that not infrequently preclude completion of standard of care chemoradiation. In the Rose, et al, study, for example, only 49% of women were able to complete all 6 intended cycles of cisplatin[6]. At present, the best strategy for managing distantly metastatic (e.g. disease occurring in the mediastinum or supraclavicular nodal basin) is unclear. Our institutional standard for women with disease outside standard pelvic and para-aortic radiation fields has been to administer 3-6 cycles of combination platinum-based chemotherapy. We then offer definitive radiotherapy to patients who experience a partial or complete response to chemotherapy treatment. Our initial analyses of the National Cancer Database (NCDB) indicate that this treatment plan significantly improves the survival of Stage IV cervical cancer patients.

2.3.1 Rationale for Study Population

The most effective strategy for managing distantly metastatic invasive carcinomas of the cervix (e.g. disease occurring in the mediastinum, bone, or supraclavicular nodal basin) is not defined. In the absence of nationally accepted guidelines, our institutional standard for women diagnosed with disease outside standard pelvic and

para-aortic radiation fields has been 3-6 cycles of induction-style carboplatin and paclitaxel. Whole pelvic radiotherapy is then offered for patients with good performance status who experience a partial or complete disease response to chemotherapy. Based on the success of niraparib in breast and ovarian cancer trials and the concern for toxicities and comorbidities limiting the compliance of concurrent cisplatin for cervical cancer, we propose a phase I/II study of women diagnosed with metastatic (Stage IV) disease to evaluate the safety, tolerability and preliminary efficacy of Niraparib when administered concurrently with definitive regional radiotherapy for treatment of cervical cancer.

2.3.2 Rationale for Objectives

Niraparib, an orally available small molecule PARP inhibitor, has been well-tolerated in Phase I/II dose-escalation trials, and is currently being investigated in Phase III trials as monotherapy for advanced breast cancer patients. At present, there is no clinical trial data available to determine whether niraparib can be safely administered concurrently with radiation. **The fundamental hypothesis of this proposal is that niraparib can be effectively used to sensitize invasive cervical cancers to radiotherapy**. Here, we propose a prospective, hybrid Phase I/II dose study to evaluate the safety and efficacy of niraparib as a potential radio-sensitizer in platinum sensitive patients. The Phase I component of this study will be used to determine a safe and tolerable dose of niraparib that can be administered concurrently with definitive regional radiotherapy for treatment of metastatic cervical cancer. The subsequent Phase II component will then evaluate the efficacy of this combination regimen, as measured in time to local disease progression.

The primary objective of the Phase I component is to determine the maximally tolerated dose (MTD) of niraparib when given concurrently with pelvic radiotherapy. The primary outcome of the Phase II component is defined as time to pelvic (local) control for patients who have received niraparib with pelvic radiation as part of their treatment for a metastatic cervical cancer. Progression will be clinically defined as local (pelvic) disease growth, as this is a standard measure of effect in cervical cancer.

2.3.3 Rationale for Measures

Maximum tolerated dose (MTD) is the highest dose of niraparib that does not cause unacceptable side effects as defined as Dose Limiting Toxicity (DLT) in more than 30% of patients; see Section 4.8. Toxicity will be reported as the frequency and grade of each toxicity determined using CTCAE, Version 4.

For the efficacy analysis, we evaluate the effectiveness of concurrent niraparib by measuring local progression free survival, which is the standard measure in cervical cancer. Local (pelvic) control will allow for evaluation of Niraparib as a radiosensitizer as the radiation will be directed to the pelvic tumor. Recurrence will be determined as the time from baseline CT or PET-CT date to pathologic or

radiologic diagnosis of any local or distant disease, receipt of any additional anti-cancer therapy, or death from any cause. Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest unidimensional measurement (diameter) of index tumor lesions are used to assess response by RECIST criteria.

Quality of life will be used to determine the prevalence and duration of acute and long-term symptoms and symptom scores using FACT-Cx.

3 PARTICIPANT SELECTION

3.1 Inclusion Criteria

a. Participant must have histologically confirmed diagnosis of invasive squamous cell or adenocarcinoma of the cervix, FIGO Stage IIIC2 or IV (see Appendix 5)

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

c. Participant must be ≥ 18 years of age

d. Participant must have adequate organ function within 28 days of registration, 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

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

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

g. Female participant of childbearing potential must have a negative serum pregnancy test within14 days prior to registration. Pregnancy test should be repeated within 7 days before CT simulation if more than 14 days has passed since the previous pregnancy test. (If serum test is falsely positive, pregnancy can be excluded by appropriate pelvic imaging.) Patient must agree to abstain from activities that could result in pregnancy from screening through completion of 7 days of pelvic radiotherapy. Females of non-childbearing potential is defined as follows (by other than medical reasons):

- ≥45 years of age and has not had menses for >1 year
- Post-hysterectomy, post-bilateral oophorectomy, post external beam radiation of 6 Gy to the pelvis, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by a physical exam or imaging.

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

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

j. Participant must have completed 3-6 cycles of platinum based chemotherapy (acceptable regimens in Appendix 7) with clinical evidence of CR (complete response) or PR (partial response) by RECIST criteria no less than 4 weeks and no greater than 12 weeks prior to initiation of protocol therapy. If bevacizumab used, 6 weeks must elapse between administration of bevacizumab and start of radiation therapy.

k. Participant must be eligible for chemoradiation treatment in the opinion of the treating investigator

l. Participants who are HIV+ must have CD4 counts >200/dL and demonstrate documented HAART compliance

m. Chemotherapy-related hematological toxicities must have resolved to Grade 1 or less

n. Participant must have had a CT (chest/abdomen/pelvis) or PET-CT, within 56 days of registration

3.2 Exclusion Criteria

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

b. Participant must not have known documented intra-uterine pregnancy

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

d. Participant must not have received an investigational therapy ≤ 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is shorter, prior to initiating protocol therapy. Participant that has received prior treatment with a PARP inhibitor is excluded from this study

e. Participant last treatment with platinum based chemotherapy was ≥12 weeks from initiation of protocol therapy

f. Participant must not receive any additional chemotherapy while on study

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 niraparib components or excipients

i. 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

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

k. 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, NYHA Class III/IV heart failure, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, or any psychiatric disorder that prohibits obtaining informed consent. Participant must not have had a CVA within 6 months of registration

l. 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 that has been definitively treated)

4 TREATMENT PLAN

4.1 Method of Treatment Assignment

Phase I component will evaluate safety for two dose levels of niraparib (100 mg and 200 mg) for use with concurrent pelvic radiotherapy. The dose assignments are shown in Table 2, based on DLT events.

Initial treatment dose is 100 mg, and then every 3 patients the dose is escalated if the observed toxicity rate at the current dose is low, de-escalated if the observed toxicity rate is high, and additional patients are treated if the observed toxicity rate is between indeterminate. Participants will continue to be enrolled and assigned to treatment dose according to these rules until 17 efficacy evaluable participants are enrolled to any single dose level.

Table 2: DLT Regulation of Dose Escalation and De-Escalation

Number of patients treated	3	6	9	12	15	18
Escalate if number of DLT <=	0	1	2	2	3	4
Treat additional 3 pts on current dose if number of DLT=	1	2	3	3, 4	4, 5	5, 6
Deescalate* if number of DLT >=	2	3	4	5	6	7
Eliminate** if number of DLT >=	3	4	5	7	8	9

* At the lowest dose level, if the recommendation is to de-escalate AND the dose level has not been eliminated from consideration, 3 additional pts will be accrued at the same dose level; otherwise the trial will stop.
** Eliminate dose level and all higher doses from further use.

Initial treatment dose is 100 mg, and will be escalated to 200 mg per Table 2

Radiation with niraparib must start within 12 weeks of finishing platinum based chemotherapy. If bevacizumab is used, a minimum of 6 weeks of time must have elapsed between the last cycle of bevacizumab and the start of radiation.

Niraparib will be administered continuously on a daily basis starting the same day as the start of radiation and continued through 28 days after completion of radiation. Niraparib dosing will be held on days of brachytherapy administration and resume the following day.

At that time, participant may continue on maintenance niraparib (28-day cycles) if the following criteria are met:

- No evidence of progressive disease (clinical disease assessment)
- Adequate performance status (0-2)

- If, in the opinion of treating investigator, participant has tolerated niraparib treatment adequately.

Maintenance niraparib may be continued until evidence of disease progression or unacceptable toxicities, based on assessments every 28 day cycle.

4.2 Treatment Regimen

Niraparib will be administered as a flat-fixed (100 mg or 200 mg), continuous daily dose. The only exception is during brachytherapy administration occurring during radiation therapy. Niraparib dosing will be interrupted on these days and resume the following day. 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 replaced or made up by altering the subsequent dose of medication taken or shortening the intervals between future doses.

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 study drug is dispensed.

4.2.1 Other Agent Administration

Radiotherapy consisting of whole pelvic radiotherapy with extended field radiotherapy will be administered to all patients as per institutional standard care. Radiotherapy to disease outside the pelvic or para-aortic field will be at the discretion of the treating physician. Extended field radiotherapy will also be administered to those subjects with documented radiologic evidence of common iliac or para-aortic lymphadenopathy. Intensity modulated radiotherapy (IMRT) will be used for all subjects, allowing definitive target coverage to be optimized while minimizing the radiation delivered to adjacent normal tissues, such as bone marrow. Here, use of IMRT should decrease both acute and chronic toxicity, as the use of IMRT has been previously shown to reduce the incidence of Grade 2 GI toxicities as well as the radiation dose delivered to active bone marrow in the pelvis. Treatment fields will be extended to the level of the renal vessels in cases where enlarged common iliac nodes have been identified, and to the diaphragmatic crura in cases of enlarged para-aortic nodes. This will consist of 45-50 Gy delivered in 1.8-2 Gy fractions, delivered with IMRT technique. Specific dose fractions used will be left to the discretion of the treating physician as long as mean bone marrow dose remains

under 36 Gy, concomitant as well as sequential nodal boost is permitted for node-positive patients. Treatments will be given on a daily basis, for 5 days a week. Brachytherapy will be delivered via either intracavitary or interstitial techniques such that the total dose to the cervical disease is 80-90 Gy from a combination of external beam and brachytherapy. Use of standard intracavitary applicators: tandem and ovoids or tandem and rings as well as interstitial brachytherapy (as needed) will be acceptable. The decision to use intercavitary radiation will be made at the time of initial imaging; i.e. if the disease would not be well covered by a standard tandem and ovoid implant, then interstitial needles will be considered. HDR brachytherapy will be used for the majority of cases, however in the case of patient preference, LDR may be considered. Computed tomography (CT) will be used to calculate dosimetry for the brachytherapy applications. All brachytherapy reporting will be performed as per ICRU guidelines, with the cumulative dose (external beam + brachytherapy) prescribed calculated in EQD2 to the high-risk clinical target volume (HR-CTV), bladder D2cc ≤90 Gy, rectal D2cc ≤ 75 Gy, bowel D2cc < 60 Gy, sigmoid D2cc<75 Gy. Doses will be converted to EQD2 doses by the formula EQD2 = D x [(d + α/β)/(2 + α/β)]. The following parameters will be recorded: D100 for HR-CTV, D90 for HR-CTV, V100 for HR-CTV.

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
- Any surgery that involves tumor lesions. Note: 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.[76]

4.4 Birth Control

Female participant of childbearing potential must have a negative serum pregnancy test within 14 days prior to registration. Pregnancy test should be repeated within 7 days before CT simulation if more than 14 days has passed since the previous

pregnancy test. (If serum test is falsely positive, pregnancy can be excluded by appropriate pelvic imaging.) Patient must agree to abstain from activities that could result in pregnancy from screening through completion of 7 days of pelvic radiotherapy. Females of non-childbearing potential is defined as follows (by other than medical reasons):

- ≥45 years of age and has not had menses for >1 year
- Post-hysterectomy, post-bilateral oophorectomy, post external beam radiation of 6 Gy to the pelvis, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by a physical exam or imaging.

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 Dose Escalation

This study will be conducted using a Bayesian Optimal Interval (BOIN) design with a target DLT rate of 0.3 (Table 2). Two dose levels of niraparib (100mg, and 200 mg,) will be evaluated for use with concurrent pelvic radiotherapy. Study will begin at dose 100mg and escalate / de-escalate according to study design rules as per Section .1.and per Table 2.

4.8 Dose-Limiting Toxicity (DLT)

4.8.1. DLT Definitions.

The following adverse events occurring during concurrent radiation therapy and niraparib administration will be considered DLTs:

- Any treatment-related Grade 4 non-hematologic clinical (non-laboratory) AE
- Any treatment-related Grade 3 non-hematologic clinical (non-laboratory) AE (except fatigue) lasting >3 days despite optimal medical intervention
- Any treatment-related Grade 3 or 4 non-hematologic laboratory abnormality if any of the following also occur:
  - The abnormality leads to hospitalization.
  - The abnormality persists for ≥7 days from the time of AE onset.
- Any treatment-related hematologic toxicity defined as any of the following:

  - Grade 4 thrombocytopenia for ≥14 days from the time of AE onset
  - Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding
  - Grade 4 neutropenia for ≥7 days, Grade 3 or 4 neutropenia associated with infection, or Grade 3 or 4 febrile neutropenia
- Any treatment-related toxicity leading to prolonged delay (>28 days) in initiating Cycle 3 of Niraparib
- Any treatment-related toxicity leading to prolonged delay or withholding of radiation therapy (>2 days)
- Any treatment-related Grade 5 AE
- Any treatment related Grade 2 AE which is severely impacting the patient's quality of life and the treating physician believes to be directly related to administration of niraparib, will be considered for dose reduction at the discretion of the treating physician and the patient.

4.8.2. DLT Rules

Niraparib dosing levels will be modified or halted as per study rules specified in Table 2.

Dose modifications for participants are in Section 5 below.

4.9 **Treatment Discontinuation**

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

- Disease progression
- Change in medical condition that deems the subject inappropriate for continued investigational therapy in the opinion of the treating investigator
- 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 becomes aware of conditions or events that suggest a possible risk or hazard to participants if the clinical study continues

4.10 **Duration of Follow Up**

Participants will be followed for 12 months after removal from protocol therapy or until death, whichever occurs first. Chart review will continue for 5 years from registration or until death, to evaluate for MDS/AML.

4.11 **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
- Lost 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 will be made to contact the participant before she is deemed lost to follow-up. These attempts will include at least 1 attempt via certified mail.

4.12 **Participant Replacement Criteria**

Not applicable.

5 DOSE MODIFICATIONS

5.1 Niraparib

Treatment may be modified for any Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 that the patient and treating physician believe to be severely impacting the patient's QOL and the treating physician believes to be directly related to administration of niraparib.

Treatment must be interrupted for any non-hematologic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib (Table 4). 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 4). If the event recurs at similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 1 dose reductions will be permitted (i.e. to a minimum dose of 100 mg QD – see 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 5. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the 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.

Table 3: Definition of Niraparib Dose Levels	
Event	**Dose**[a]
If Initial dose is at highest level	200[b] mg QD
DL-1: First dose reduction for treatment-related CTCAE Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible (or Grade 2 at the discretion of the treating physician)	100 mg QD
Continued treatment-related CTCAE Grade 3 or 4 AE or SAE lasting >28 days (or Grade 2 at the discretion of the treating physician)	Discontinue niraparib.

[a] Dose not to be decreased below 100 mg daily.
[b] If the initial dose is below 200 mg, the same dose reduction principles will apply with fewer dose modification steps available.

Table 4: Niraparib Dose Modifications for Non-hematologic 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. Up to 1 dose reductions are permitted.
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue niraparib.

Table 5: Niraparib Dose Modifications for Hematologic Toxicity	
Laboratory Abnormality	**Intervention**
Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time.	
Platelet count < 75,000/μL	First occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥75,000/μL. Resume niraparib at reduced dose.[a] 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 ≥1,000/μL. Resume niraparib at a reduced dose.[a] 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 dose reduction to 100 mg QD.
Hemoglobin < 8 g/dL	Withhold niraparib for a maximum of 28 days and monitor blood counts until hemoglobin returns to >8 g/dL. Resume niraparib at a reduced dose.[a] 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 dose reduction to 100 mg QD. Any patient requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a dose reduction upon recovery if study treatment is resumed

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 once platelet count ≥75,000.[a]
Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.

[a] Niraparib dose must not be decreased below 100 mg daily. Additional details on dose reduction are described in Table 3

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 ≥75,000/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 as described in Table 5 above. To ensure the safety of the new dose, blood draws for CBC will be done as per study protocol.

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.

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

6.1.2 Potential Risks of Niraparib

Reference the currently approved Investigational Brochure for niraparib to obtain safety, efficacy and potential risk information for the drug.

6.1.3 Packaging, Labeling and Storage

Niraparib is supplied by TESARO 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 and managed in an Investigational Pharmacy in compliance with GCP.

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-Investigator 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 will be destroyed at the investigational site at study conclusion and after all final drug accountability activities have been completed.

6.2 Other Agent

Not applicable

7 CORRELATIVE STUDIES

Table 6: Summary of Research Tissue and Blood Specimen Collection

Research Sample	Time point	Contents
Blood	**Cycle 1 Day 1**	
	Pre-Dose	2- 5mL EDTA Purple Top
	2 hours (+/- 15 min) post-dose	2- 5mL EDTA Purple Top
	Cycle 1 Day 8	
	Pre-Dose (within 30 min of dose)	2- 5mL EDTA Purple Top
	2 hours (+/- 15 min) post-dose	2- 5mL EDTA Purple Top
	Cycle 1 Day 22	
	Pre-Dose (within 30 min of dose)	2- 5mL EDTA Purple Top
	2 hours (+/- 15 min) post-dose	2- 5mL EDTA Purple Top

7.1 Pharmacodynamics (PARP Testing)

Blood samples (10 cc total whole blood) will be collected in 2 (two) lavender top tubes on Days 1, 8, and 22 of niraparib treatment. For Cycle 1 Day 8 and Cycle 1 Day 22, specimens will be collected both pre-dose (within 30 minutes of dose) as well as 120 + 15 minutes post-dose of niraparib. All specimens will be collected in EDTA lavender top tubes. Once collected, specimens will be placed on ice and transported to designated laboratories. After isolating peripheral blood mononuclear cells using standard clinical protocol, specimens will be flash frozen and stored at -80˚C until biochemical analysis of PARP activity is performed. At the time of batched analyses, specimens will be thawed and lysed, after which enzymatic PARP activity will be measured using a commercially available assay previously validated for this purpose (PARP In Vivo Pharmacodynamic Assay, Trevigen, Inc., Catalog #4520-096-K). All testing will be performed as in triplicate with results reported as mean percent inhibition of PARP1/2 activity at experimental time points (Day 1 post-dose and Days 8 and 22) compared to baseline (Day 1 pre-dose). Mean values with standard deviation will be calculated and reported for each time point. Two-tailed Student's T-tests will be used to assess the statistical significance of observed differences. Associations between PARP inhibition and 12-month progression free survival will be evaluated using Kaplan Meier analysis where statistically feasible. Any specimens remaining after the conclusion of these

analyses will be preserved until study closure, after which they will be destroyed as per relevant institutional protocols. Bioanalytes prepared from these specimens will also be destroyed.

8 SCHEDULE OF ASSESSMENTS

8.1 Screening

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

- Informed Consent
- Review of Inclusion/Exclusion Criteria
- ECOG Performance Status
- Physical Exam
- Pelvic Exam
- HBV/HCV test
- Medical History and concomitant medications
- Vital Signs: systolic and diastolic blood pressures, weight and temperature
- Height
- Pregnancy testing within 14 days prior to registration; repeated as needed to comply with Inclusion/Exclusion Criteria
- CBC with plat/diff
- Comprehensive metabolic panel
- CT (chest/abdomen/pelvis) or PET-CT, within 56 days of registration.
- Baseline QOL assessment

Please note that treatment with niraparib would not be scheduled to begin <4 weeks from most recent dose of cytotoxic chemotherapy (e.g. carboplatin and paclitaxel).

8.2 During Radiation (Niraparib given continuously)

Radiation is given via external beam daily 5 days/week for 5 weeks and then brachytherapy for 2 weeks. Niraparib is given continuously on a 28 day cycle. Niraparib dosing will be held on days when brachytherapy is administered and dosing will resume the following day.

The following procedures/tests will be performed on Day 1 (+/- 3 days) of each cycle:

- Vital signs: systolic and diastolic blood pressures, weight, and temperature
- Comprehensive metabolic panel
- PARP testing: Days 1, 8, and 22.

- Assess for MDS/AML (assessed by chart review): Week 1 only

The following procedures/tests will be performed weekly during concurrent radiation therapy and niraparib administration:

- Physical Exam
- CBC with plat/diff
- Adverse event monitoring
- QOL Assessment

8.3 Maintenance Therapy (after completion of radiation)

The following procedures/tests will be performed at a study visit 28 days (+/- 7 days) after completing radiation therapy (XRT completion) and at each Maintenance visit (every 28-days):

- Physical Exam
- Pelvic Exam (only performed every 3 months)
- Vital signs: systolic and diastolic blood pressures, weight, and temperature
- CBC with plat/diff
- Comprehensive metabolic panel
- Adverse event monitoring
- Review of concomitant medications (only at the completion of radiation therapy and XRT completion visit)
- ECOG Performance Status (at XRT completion visit, and at least every 3 months during maintenance)
- QOL Assessment
- Assess for MDS/AML (assessed by chart review)

8.4 End of Treatment

The following procedures/tests will be performed at the End of Treatment visit, which must occur within 28 days (+/- 7 days) from the last administered dose of niraparib:

- Adverse event monitoring
- CBC with plat/diff
- Comprehensive metabolic panel

- QOL Assessment (if the End of Treatment visit occurs during the maintenance phase)
- Assess for MDS/AML (assessed by chart review)

8.5 Follow-up

The following procedures/tests will be performed every 3 months (+/- 14 days) for one year from the end of treatment:

- Physical Exam
- Pelvic Exam
- CBC with plat/diff
- Comprehensive metabolic panel
- Adverse event monitoring
- CT (chest/abdomen/pelvis) or PET-CT
- QOL Assessment
- Assess for MDS/AML (assessed by chart review)

8.6 Long Term Follow-up

The following procedures/tests will be performed every 12 months (+/- 2 months) for five years or until death, whichever occurs first:

- Survival assessment
- Assess for MDS/AML (assessed by chart review)

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-Investigator and TESARO 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 registration unless otherwise specified in Inclusion/Exclusion Criteria. 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.

For women of childbearing potential, as defined in the eligibility criteria, a pregnancy test must be completed within 14 days of registration. Pregnancy testing will be repeated within 7 days prior to CT simulation if it has been more than 14 days has elapsed since the last pregnancy test.

Baseline assessments must be performed prior to administration of any study agent. See Study Calendar footnote A for relevant windows within which to perform all other protocol-dictated assessments.

		Niraparib + Radiotherapy (Weekly)[A]								Maintenance (after XRT) (28 Day Cycles)		Follow-Up (after study drug)		Long Term Follow up
	Base-line	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Post XRT (28 days after treatment)	Maintenance every 28-days[C]	EOT Visit[D]	Follow-Up, every 3 months for 1 year[E]	(Chart Review Only) Until 5 years after radiotherapy completion
SCREENING														
Written Informed Consent	X													
Inclusion/Exclusion Criteria	X													
PHYSICAL														
Medical History, Previous Medications[B]	X													
Physical Exam	X	X	X	X	X	X	X	X	X	X	X		X	
Vital Signs and Weight	X	X				X				X	X			
Height	X													
ECOG Performance Status	X									X	X[M]			
Pelvic Exam	X									X	X[Q]		X	
HBV/HCV test	X													
LABORATORY														
CBC with plat/diff	X	X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Metabolic Panel[F]	X	X				X				X	X	X	X	
Pregnancy test[G]	X													
ASSESSMENTS														
Adverse Events/Toxicity[H]		X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X									X				

CT (chest/abdomen/pelvis), or PET-CT	X[I]											X	
QOL Assessment, FACT-Cx	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess for MDS/AML[J]		X								X		X	X	X[N]
DLT Assessment									X[O]					
CORRELATIVE STUDIES														
PARP testing[K]		X	X		X									
Bone marrow aspirate and biopsy if needed[L]		X												
TREATMENT														
Niraparib		Continuous, Daily[P]												
Radiotherapy		X	X	X	X	X	X	X						

(A) Allowed windows are based upon frequency of the assessment, as follows. Weekly assessments: +/- 3 days; 28-day assessments: +/- 7 days; Q3-month assessments: +/- 14 days.
(B) Medical History should include all prior anticancer therapy.
(C) After completing radiotherapy, subject may continue on niraparib per Section 4.1. Drug is administered in 28-day cycles, and may continue until the criteria in Section 4.1 is met to discontinue treatment.
(D) After stopping niraparib, subjects will have an End of Treatment visit within 28 days of stopping study drug.
(E) After stopping niraparib, patients will be followed every 3 months for 1 year after stopping niraparib. Post-niraparib visits: 3, 6, 9 and 12 months.
(F) Must include: bilirubin, AST, ALT, serum creatinine, sodium, potassium, chloride, CO_2, blood urea nitrogen (BUN), glucose. At pre-study, bilirubin is required for eligibility. See Section 3.
(G) Female subjects of childbearing potential as defined in the eligibility criteria must have a serum pregnancy test within 14 days of registration. Pregnancy test must be repeated ≤ 7 days prior to CT simulation if more than 14 days has elapsed since the last pregnancy test.
(H) Physician will use NCI CTCAE scale. AEs will be graded and recorded.
(I) Baseline imaging must be within 56 days of registration.
(J) MDS/AML follow-up: Chart review to evaluate for MDS or AML diagnosis.

(K) Peripheral blood mononuclear cells will be collected for PARP testing on Days 1, 8, and 22. See Section 7.
(L) For any patient suspected for MDS/AML while on study, assessments should be conducted as per standard clinical care, such as bone marrow aspirate/biopsy. 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 communicated to Tesaro, if applicable.
(M) At minimum, the Performance Status must be assessed by the investigator every 3 months during maintenance.
(N) Chart review should be conducted every 12 months (+/- 2 months) for five years after the completion of radiotherapy.
(O) DLT assessment is not a subject visit, but a study evaluation point. DLT assessment will occur for all subjects upon completion of concurrent radiation therapy and niraparib administration. Study staff will use the outcome of DLT assessment to determine dose level determination for subsequent study enrollment.
(P) Niraparib administration will be given continuously on 28-day cycles, except during HDR brachytherapy when niraparib dosing is held.
(Q) During Maintenance, pelvic exam is only required every 3 months.

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.

The term “unexpected” refers to an event or reaction that is not listed in the current investigator’s brochure or approved Informed Consent Form as a possible risk or discomfort or is not listed at the specificity or severity that has been observed.

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 Events of Special Interest

An Adverse Events 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 by the Investigator to the Sponsor-Investigator and TESARO 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
- Embryo-fetal toxicity

AESI should be collected and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the PI and TESARO upon awareness for any patient who has received niraparib (regardless of the timeframe since the last dose).
- Pneumonitis should be reported to the Sponsor-Investigator and TESARO 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 occurs with a TESARO product, the Sponsor-Investigator and TESARO 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).

10.4 Reporting Special Situations:

All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure associated with a TESARO product must be reported on an SAE Report Form to the Sponsor-Investigator and to TESARO 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-Investigator and to TESARO within 24 hours of awareness.

10.5 Assessment of Adverse Events

Each AE will be assessed by the investigator with regard to severity and causality with regard to study treatment as outlined below.

10.5.1 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.

10.5.2 Relationship to Study Drug

The Investigator must provide a causality assessment regarding the relationship of the event with the study drug and/or study procedure for all AEs. One of the

following categories should be selected based on medical judgment, considering all contributing factors:

- **Related**: The AE is *clearly related* to the study treatment/medicinal product.
- **Probably Related:** The AE is *likely related* to the study treatment/medicinal product.
- **Possibly Related:** The AE *may be related* to the study treatment/medicinal product.
- **Not Likely Related:** The AE *is doubtfully related* to the study treatment/medicinal product.
- **Not Related**: The AE is *clearly NOT related* to the study treatment/medicinal product.

10.6 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 ended question such as, “How have you been feeling since your last study visit?” The Investigator or designee 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 start of treatment for this study through 30 days post treatment and reported accordingly. SAEs considered by the Investigator to be related to study medication are reported throughout the Follow-up Assessment Period.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, or reported by patient), will be documented for each patient from the time of treatment assignment through the final follow-up visit.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the Treatment Period. Pre-existing conditions will be recorded as Medical History.

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

10.7 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.

10.8 Reporting to the Sponsor-Investigator

All SAEs and AESIs must be reported to the Sponsor-Investigator 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.

Sponsor-Investigator SAE, AESI Reporting Information
Michelle S. Ludwig, MD, MPH, PhD Email: Michelle.Ludwig@bcm.edu Telephone: (713) 566-3757

10.9 Reporting to TESARO

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

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

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

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

On a monthly basis, the Sponsor-Investigator will provide TESARO with a line listing of all SAEs/AESIs that have been reported to date. On at least an annual basis, the Sponsor-Investigator will provide a copy of the safety reports submitted to applicable

Regulatory Authorities or IECs. Annual reports should be provided to TESARO within 3 business days of submission to the applicable regulatory body.

TESARO's practice is to acknowledge receipt of all safety information within 72 hours. The Sponsor-Investigator should resend any materials that are not acknowledged within this time period.

10.10 Quarterly AE/SAE Reporting to TESARO

On a quarterly basis the Sponsor-Investigator will provide TESARO 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.

10.11 Pregnancy

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

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

Each pregnancy must be reported on a Pregnancy Notification 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-Investigator and TESARO within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

10.12 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Per regulatory requirements, if an event is assessed by the Sponsor-Investigator as a Serious Unexpected Suspected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor-Investigator to submit the SUSAR to the appropriate Regulatory Authorities according to applicable regulations, as outlined in the following sections.

10.12.1 Reporting of SUSARs to the FDA

Serious adverse events that are determined by the sponsor to be a SUSAR will be reported to the FDA as an IND Safety Report within 15 calendar days of sponsor's awareness of the event.

Unexpected fatal or life-threatening suspected adverse events will be reported to the FDA as an IND Safety Report within 7 calendar days of sponsor's awareness of the event.

Follow up information pertaining to a previously submitted IND Safety Report will be submitted as soon as available and no later than 15 calendar days after sponsor's awareness of the information.

These reports will be submitted using Form 3500A.

10.12.2 Reporting to IRB

Adverse events will be reported to the Institutional Review Board (BCM IRB) according to their reporting requirements and required time frame.

Any event that is reportable to the BCM IRB must also be reported to the DLDCCC Data Review Committee (DRC) via the Patient Safety Officer at dldcc-pso@bcm.edu.

10.13 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-investigator or qualified designee to TESARO QA at TESARO.QA@gsk.com. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

11 DATA REPORTING

11.0 Data submission

All subject data will be abstracted from the electronic medical record available for each enrolled patient and documented in an electronic database created for this study using OnCore, the proprietary, HIPAA-compliant software used by Baylor College of Medicine for these purposes. The specific demographic data to be abstracted are specified in Section 6.2. Each subject will be assigned a study code to facilitate subsequent coding of the data set once complete. This number will be used to link any primary source data stored in the HIPAA-compliant electronic database used for this study.

11.1 Data and Safety Monitoring

This study will be reviewed regularly by the Data Review Committee (DRC) of the Dan L. Duncan Comprehensive Cancer Center. The DRC will monitor the study for progress and enrollment, toxicities, adverse events, and soundness of data.

The frequency of data review by the DRC is determined by the Protocol Review and Monitoring Committee at the time of initial review and is based on the level of risk to the study subjects. Review will occur at a minimum of once each year after activation. Information reviewed by the committee includes:

a. Overall protocol accrual and expected number of patients to be treated
b. Patient registrations with regard to eligibility and evaluability
c. All adverse events and their relationship to the protocol therapy (e.g. by dose level, treatment arm, etc.) in order to determine if participants are being exposed to unanticipated or excessive toxicity
d. All serious adverse events or unanticipated problems requiring expedited reporting as defined in the protocol
e. Results of any planned interim analyses
f. Response evaluations, if relevant
g. Any issues with protocol conduct or compliance
h. Status of participation rate in correlative biology and/or imaging studies, if applicable
i. Study amendments or modifications that may have occurred since last review
j. Date of next planned review

11.2 Audits

All study documents (both source and abstracted) will be made available for inspection by and/or other relevant state and/or federal regulatory authorities as applicable with 48 hours of advance notice. The principal investigators, co-investigator and study personnel will also make themselves available upon 48 hour notice at the request of TESARO and/or any relevant institutional state and/or federal authorities.

11.3 **Data Quality Assurance**

This study will be monitored by the DLDCCC Quality Assurance program for study conduct and quality of data, according to CTSU policy. Protocol compliance, eligibility verification, informed consent procedure verification, and data accuracy will be monitored.

12 STATISTICAL METHODS

12.1 Study Design and Endpoints

This is a single arm combination Phase I/II trial of niraparib to evaluate the safety and efficacy of niraparib administered concurrently with whole pelvic radiation for patients who present with metastatic cervical cancer. Design ensures enrollment of the required number of patients for efficacy endpoint (phase II component), while continuously monitoring safety, ensuring correct selection of the MTD and allocation of maximum number of patients to the MTD group (phase I component)

12.2 Primary Endpoint

The primary endpoint of the Phase I component is to determine the MTD of niraparib when given concurrently with pelvic radiotherapy.

The primary endpoint of the Phase II component is defined as 12 month pelvic (local) control for patients who have received 1 or more doses of niraparib with pelvic radiation as part of their treatment for a metastatic cervical cancer.

Progression event will be defined as local (pelvic) disease progression as determined by the investigator, and may be clinical, radiological, or pathological. If the patient receives subsequent oncologic therapy, then the date of failure will be their visit prior to initiating therapy. Patients with no event (e.g. disease free) will be censored at the time of last contact. Local progression-free survival is measured from the time of treatment initiation to progression.

Recurrence will be determined as the time from baseline CT or PET-CT date to pathologic or radiologic diagnosis of any local or distant disease, receipt of any additional anti-cancer therapy, or death from any cause. Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

12.3 Secondary Endpoints

1: Assess the acute toxicity profile of niraparib administered concurrently with whole pelvic radiotherapy according to the CTCAE version 4 as well as the grade of each toxicity.

2: Assess quality of life for women receiving niraparib concurrently with whole pelvic radiotherapy.

3: Assess tumor response outside the radiation field using RECIST 1.1 for women receiving niraparib concurrently with whole pelvic radiotherapy.

12.4 Sample size, Accrual Rate and Study Duration

This study will be conducted using a Bayesian Optimal Interval (BOIN) design with a target DLT rate of 0.3 (Table 2). This design has algorithmic escalation/de-escalation rules easy to implement like a traditional 3+3 design but allows for specification of the target DLT rate, different size cohorts, is more likely to correctly select the MTD and allocate more patients to the MTD (see simulation results in Table 7) and expands consistent toxicity monitoring to the entire cohort. Calculations were done using R package BOIN (version 2.4, 2016 May 11, available from https://cran.r-project.org/web/packages/BOIN/index.html)

12.5 Phase I component considerations.

The study is designed to escalate the dose if the observed toxicity rate at the current dose is <= 0.2365, and de-escalate the dose if the observed toxicity rate at the current dose is >= 0.3585. If the observed toxicity rate is between 0.2365 and 0.3585, additional patients will be treated at the current dose. For cohorts of size 3, the decision boundaries are shown in Two doses levels of niraparib (100mg and 200 mg) will be evaluated for use with concurrent pelvic radiotherapy. Study will begin at dose 100mg and escalate / de-escalate according to study design rules described.

Table 7: Simulations for study design justifications

Scenarios	Dose	True DLT Rate	BOIN (Phase I/II)			Phase I "3+3"		Phase I "3+3" + Phase II		
			Fraction Treated	MTD selected	average # of patients	Fraction Treated	MTD selected	Fraction Treated[#]	% evaluated for safety	average # of patients
1. Very safe	<100mg			0.0%	21.8		2.8%			22.8
	100mg	0.05	0.18	0.8%		0.51	18.0%	0.17		
	200mg	0.15	0.82	**99.2%**		0.49	**79.2%**	0.83	20.3%	
2. Intermediate safe	<100mg			1.1%	23.4		20.1%			23.2
	100mg	0.15	0.33	16.6%		0.61	31.1%	0.22		
	200mg	0.25	0.69	**82.3%**		0.39	**48.8%**	0.78	13.8%	
3. Safe at low doses only	<100mg			3.6%	24.0		33.5%			21.3
	100mg	0.2	0.64	**77.0%**		0.71	**54.3%**	0.88	27.6%	
	200mg	0.5	0.36	19.4%		0.30	12.2%	0.12		
4. Unsafe	<100mg			**89.3%**	8.9[*]		**95.7%**		[*]	4.3[*]
	100mg	0.6	0.96	10.7%		0.97	4.0%			
	200mg	0.7	0.04	0.0%		0.03	0.3%			

[*] stopped early for safety [#] If MTD chosen correctly

12.6 Phase II component considerations.

The cohort treated at the MTD will enroll patients to the total of 17 patients needed for the evaluation of improvement in time to local progression-free survival. We have comprehensively reviewed local control outcomes for all women treated for a locoregionally advanced cervical cancer (bulky FIGO III- IVA) with chemoradiotherapy to include standard of care concurrent cisplatin at the Harris Health System between April, 2008 and April, 2015. Twelve month local progression-free survival for patients who presented with FIGO IIIA-IVA cervical cancer who receive less than the 6 cycles of standard of care concurrent cisplatin is 52%. Since this clinical trial is in a more advanced stage of population, we estimate that the local control would be 50% with standard of care and we will consider the trial a success if it is better than a 70% at 12 months. The criterion for significance (alpha) has been set at 0.10. The test is 1-tailed, which means that an effect in one direction (improvement) is expected and will be interpreted. Calculation are based on the assumptions of uniform accrual over time, exponentially distributed death times, and use of the exponential MLE test. With the proposed sample size of 17 patients, accrued over 2 years and followed for at least 1 year, the study will have power of 80% to yield a statistically significant result.

Total study sample size.

This study will enroll at least 3 patients at each dose level and at least 17 patients at the MTD level. Participants will continue to be enrolled and monitored for toxicity according to the rules specified above until 17 efficacy evaluable participants have been enrolled to any single dose level. For the purposes of this analysis, a subject is considered evaluable for the primary endpoint after completing at least one dose of niraparib. It is expected that all dose levels will be safe and assuming that even the highest dose level has a DLT rate substantially lower than the target (i.e. <10%), which is what we expect, we will have more than 99% chance of selecting the top dose level at the end of the trial. In this case the total number of patients enrolled would be 20 (3+17). Simulations of other scenarios are shown in Table 7. The maximum number that will be needed would be 24.

Adjusting for missing data

When evaluating our data from the past 6 years, we found that none of the patents were lost to follow-up, so a conservative adjustment of less than 10% (i.e. additional 2 patients) is used for the total of up to 22-27 patients. All efforts will be made via chart review to obtain information regarding missing data.

Accrual Rate

Given the large number of women with metastatic advanced cervical cancer treated at our center, we anticipate that we should be able to accrue 10 patients per year. As such, accrual to take no longer than 2 years with planned study completion within an upper limit no longer than 3 years.

Stratification Factors

Not applicable

Interim Monitoring Plan

The BOIN design requires continued toxicity monitoring. No interim data analyses are planned for efficacy endpoint.

Analysis of Primary Endpoints

The primary objective of the Phase I component is to determine the MTD based on DLT (as described previously) of niraparib when given concurrently with pelvic radiotherapy. The dose enrolling required 17 patients according to rules described in Table 2 will be determined to be the MTD. The posterior DLT rate and 95% confidence interval will be estimated using all toxicity evaluable cases.

For the efficacy analysis, we evaluate the effectiveness of concurrent niraparib by measuring local progression free survival using the exponential MLE test at alpha=0.05 level. Descriptive and summary statistics will be computed for demographic and clinical data of all subjects enrolled in the study. A Kaplan-Meier plot will be constructed to illustrate the progression-free survival trends observed.

Analysis of Secondary Endpoints

Toxicity will be reported as the frequency of each toxicity according to the CTCAE version 4.0 as well as the grade of each toxicity. Overall survival will be analyzed by Kaplan-Meier method. The associations between biological measurements and recurrence-free survival will be analyzed by the Cox regression. Quality of life will be used to determine the prevalence and duration of acute and long-term symptoms and symptom scores using FACT-Cx. FACT-Cx is used as the quality of life measure as this is our current departmental standard for all cervical cancer patients and there is no cost to use the instrument. The FACT Cx is commonly used in GOG/NRG studies. The tumor response rate (and corresponding confidence intervals) outside of the radiation field will be reported using RECIST 1.1. All of these analyses will be considered exploratory in nature.

13 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

13.0 Good Clinical Practice

This study will be conducted according to the principles of respect for persons, beneficence, and justice as stated in the Belmont Report. This study will also embrace the principles set forth in the Declaration of Helsinki. Investigators will comply with the provisions for the protection of the rights and welfare of human research subjects set forth in the U.S. Code of Federal Regulations, Title 45 Part 46, and in compliance with determinations of all Institutional Review Boards (IRBs) overseeing the research. All institutions participating in the protocol will have in place a Federal Wide Assurance (FWA) with the DHHS Office of Human Subjects Research Protections. This assurance documents the institution's commitment to the human subjects regulations.

The study will also be conducted under Good Clinical Practice (GCP) as laid out in the International Conference on Harmonisation (ICH) E6 GCP Consolidated Guidance (ICH 1996). Investigator responsibilities are set out in Section 4 of the E6 Guideline (as published in the Federal Register May 1997). Sponsor responsibilities are set out in Section 5 of the E6 ICH Guideline (as published in the Federal Register May 1997).

13.1 Informed Consent

The informed consent document will be reviewed and approved by the IRB responsible for protecting the safety and welfare of subjects participating in research. Informed consent will be obtained from research participants by the PI or other staff with appropriate training and documentation of task delegation.

13.2 Protocol Approval and Amendment

The principal investigator will obtain permission from the local Institutional Review Board and/or all other regulatory or monitoring committees required to initiate study activities prior to subject enrollment. Study amendments will be propagated by submission first to TESARO, Inc. Once approved, amendments will be submitted in a timely fashion to IRB, FDA and/or all other regulatory committees for evaluation and approval prior to modifying study conduct. No modifications to the study protocol will be allowed without TESARO approval and/or subsequent approval of applicable IRBs.

13.3 Investigator Responsibilities

The investigator is responsible for conducting studies in accordance with the protocol. The investigator will ensure that there is adequate training for all staff participating in the conduct of the study and will supervise study tasks performed by the staff. The investigator is also responsible for protecting the rights, safety and welfare of subjects under their care.

13.4 Subject Confidentiality and Data Protection

Confidentiality of all protected health information will be strictly maintained for all subjects enrolled in this protocol. The HIPAA-compliant electronic database used to abstract demographics, laboratory values and/or all other clinical data required by this protocol is maintained on a limited-access, password protected server maintained by BCM and/or BCM affiliates (HIPAA-compliant covered entities) specifically for this purpose. Access to this database as well as the server requires the use of Citrix-supported software designated for this purpose. Furthermore, access to the server and database require active passwords issues by Baylor College of Medicine for this purpose. Copies of any written documentation containing PHI will be maintained within locked file cabinets within the Dan L. Duncan Comprehensive Cancer Center. Access to the areas where these file cabinets are stored requires photo identification, which is routinely verified by BCM Security upon entering the campus.

13.5 Access to Source Documents

Source documentation will be maintained according to standard practice within the Clinical Trials Support Unit at the Dan L. Duncan Comprehensive Cancer Center. Access to support documentation maintained within the CTSU will be provided to appropriate state, federal or local authorities as required by law. In addition, access to source documentation will be provided to the study collaborator (Tesaro, Inc.) as requested, in accordance with HIPAA and all other appropriate institutional policies and procedures.

13.6 Archival

Study records will be maintained securely for a minimum of at least 3 years as per relevant institutional, state and federal requirements.

13.7 Publications

Study investigators reserve the right to communicate and publish study outcomes. To this end, the principal investigator will be responsible for the preparation and submission of all abstracts, presentations and manuscripts summarizing study outcomes, in collaboration with other study investigators.

14 REFERENCES

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APPENDIX 1 – PERFORMANCE STATUS

ECOG PS	KARNOFSKY PS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all self care 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 self care; 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 self care; 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.
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Available at: http://ecog-acrin.org/resources/ecog-performance-status

APPENDIX 2 – RESPONSE CRITERIA

Summary of the Response Evaluation Criteria In Solid Tumours (RECIST) 1.1

A baseline scan is performed not more than one month before the start of treatment. Subsequent response to treatment is evaluated against this scan or the subsequent scan demonstrating the lowest sum of target disease (nadir).

Target lesions are defined at baseline and must be ≥ 10 mm in longest diameter or ≥ 15 mm in short axis if the lesion is a lymph node (although lymph nodes ≥ 10 mm are considered pathological, but non-measurable). If the CT slice thickness is > 5 mm, the extranodal disease must be ≥ twice the slice thickness. Measurable disease on a chest radiograph is ≥ 20 mm, provided the lesion is "clearly defined and surrounded by aerated lung" (1).

A maximum of 5 lesions may be chosen, with a maximum of 2 per organ. The sum of all the extra-nodal long axis measurements and nodal short axis measurements is calculated. When analysing a follow up scan, the same lesions are measured and the sum of target disease is again calculated. Measurements need not be along the same axis (as measured at baseline), but should always be the longest axis of the lesion at that point in time. It does not even have to be at the same slice position, provided the measurement is of the same lesion. However, if the initial measurements are in the axial plane, all further measurements of that lesion must remain in the axial plane. Likewise, if the initial measurements are in the coronal plane (this is acceptable), all further measurements of that lesion must be in the coronal plane.

Bone lesions with a soft tissue component ≥ 10 mm can be designated as target lesions. Sclerotic bone lesions cannot be used. Although solid lesions should be used in preference, cystic lesions may be used provided they represent the disease being studied.

If a lesion disappears, the measurement of that lesion is clearly 0 mm, however, if the lesion remains present, but is too small to measure accurately, a default measurement of 5 mm should be given. If lymph nodes decrease to < 10 mm, these are considered to be disease free, but remain target lesions (until new target lesions are selected - usually when disease has progressed and a new baseline scan is performed prior to a change in treatment). If lesions merge, the long axis of the resulting lesion is measured as one lesion in place of the individual lesions. If lesions split, the long axis of each individual lesion is added.

An increase of ≥ 20% from the nadir (or baseline, if it represents the point at which the sum of target disease was lowest) represents progressive disease. If the burden of non-target or non-measurable disease increases unequivocally, then progressive disease may be declared, but the increase really must be unequivocal. If a new lesion appears, progressive disease is declared. If, for example, there is doubt as to whether a lesion is new or, say, inflammatory change, follow up scans are required. If the new lesion is confirmed, the date of progression is taken to be the date on which the new lesion was first detected.

A decrease in the sum of target disease of ≥ 30% represents partial response.

Stable disease lies between partial response and progressive disease.

Complete response is the disappearance of all lesions with nodes measuring < 10 mm and normal tumour markers.

If a lesion reappears after disappearing in a patient with complete response, progressive disease is declared. However, if such a lesion behaves in this manner in a patient with stable disease or partial response, it is the change in sum of target disease that defines the response or progression.

PET-CT and MR may be used. The main specification is that imaging protocols are consistent throughout the trial. Therefore, contrast timings, MR sequences and planes should remain the same.

APPENDIX 3: QOL FORM (ENGLISH)

FACT-Cx (Version 4)

Below is a list of statements that other people with your illness have said are important**.** **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4

Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.* ☐					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
Cx1	I am bothered by discharge or bleeding from my vagina	0	1	2	3	4
Cx2	I am bothered by odor coming from my vagina	0	1	2	3	4
Cx3	I am afraid to have sex	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
Cx4	My vagina feels too narrow or short	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
Cx5	I am afraid the treatment may harm my body	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
BL1	I have trouble controlling my urine	0	1	2	3	4
BL3	It burns when I urinate	0	1	2	3	4
Cx7	I have discomfort when I urinate	0	1	2	3	4
HN1	I am able to eat the foods that I like	0	1	2	3	4

APPENDIX 4: QOL FORM (SPANISH)

A continuación encontrará una lista de afirmaciones que otras personas con su misma enfermedad consideran importantes. Marque un solo número por línea para indicar la respuesta que corresponde a los últimos 7 días**.**

	ESTADO FÍSICO GENERAL DE SALUD	**Nada**	**Un poco**	**Algo**	**Mucho**	**Muchí-simo**
GP1	Me falta energía	0	1	2	3	4
GP2	Tengo náuseas	0	1	2	3	4
GP3	Debido a mi estado físico, tengo dificultad para atender a las necesidades de mi familia.	0	1	2	3	4
GP4	Tengo dolor	0	1	2	3	4
GP5	Me molestan los efectos secundarios del tratamiento	0	1	2	3	4
GP6	Me siento enfermo(a)	0	1	2	3	4
GP7	Tengo que pasar tiempo acostado(a)	0	1	2	3	4

	AMBIENTE FAMILIAR Y SOCIAL	**Nada**	**Un poco**	**Algo**	**Mucho**	**Muchí-simo**
GS1	Me siento cercano(a) a mis amistades	0	1	2	3	4
GS2	Recibo apoyo emocional por parte de mi familia	0	1	2	3	4
GS3	Recibo apoyo por parte de mis amistades	0	1	2	3	4
GS4	Mi familia ha aceptado mi enfermedad	0	1	2	3	4
GS5	Estoy satisfecho(a) con la manera en que se comunica mi familia acerca de mi enfermedad	0	1	2	3	4
GS6	Me siento cercano(a) a mi pareja (o a la persona que es mi principal fuente de apoyo)	0	1	2	3	4
Q1	Sin importar su nivel actual de actividad sexual, conteste a la siguiente pregunta. Si prefiere no contestarla, marque esta casilla y continúe con la siguiente sección. ☐					
GS7	Estoy satisfecho(a) con mi vida sexual	0	1	2	3	4

Marque un solo número por línea para indicar la respuesta que corresponde a los últimos 7 días.

	ESTADO EMOCIONAL	**Nada**	**Un poco**	**Algo**	**Mucho**	**Muchí-simo**
GE1	Me siento triste	0	1	2	3	4
GE2	Estoy satisfecho(a) de cómo me estoy enfrentando a mi enfermedad	0	1	2	3	4
GE3	Estoy perdiendo las esperanzas en la lucha contra mi enfermedad	0	1	2	3	4
GE4	Me siento nervioso(a)	0	1	2	3	4
GE5	Me preocupa morir	0	1	2	3	4
GE6	Me preocupa que mi enfermedad empeore	0	1	2	3	4

	CAPACIDAD DE FUNCIONAMIENTO PERSONAL	**Nada**	**Un poco**	**Algo**	**Mucho**	**Muchí-simo**
GF1	Puedo trabajar (incluya el trabajo en el hogar)	0	1	2	3	4
GF2	Mi trabajo me satisface (incluya el trabajo en el hogar)	0	1	2	3	4
GF3	Puedo disfrutar de la vida	0	1	2	3	4
GF4	He aceptado mi enfermedad	0	1	2	3	4
GF5	Duermo bien	0	1	2	3	4
GF6	Disfruto con mis pasatiempos de siempre	0	1	2	3	4
GF7	Estoy satisfecho(a) con mi calidad de vida actual	0	1	2	3	4

	OTRAS PREOCUPACIONES	**Nada**	**Un poco**	**Algo**	**Mucho**	**Muchí-simo**
Cx1	Me molesta el flujo o sangrado por la vagina	0	1	2	3	4
Cx2	Tengo un olor vaginal que me molesta	0	1	2	3	4
Cx3	Tengo miedo de tener relaciones sexuales	0	1	2	3	4
B4	Me siento físicamente atractiva	0	1	2	3	4
Cx4	Siento la vagina muy estrecha o pequeña	0	1	2	3	4
BMT7	Estoy preocupada por mi capacidad de tener hijos	0	1	2	3	4
Cx5	Tengo miedo de que el tratamiento pueda hacerle daño a mi cuerpo	0	1	2	3	4
BL4	Me interesa el sexo	0	1	2	3	4
C7	Me gusta mi apariencia personal	0	1	2	3	4
Cx6	Me molesta el estreñimiento	0	1	2	3	4
C6	Tengo buen apetito	0	1	2	3	4
BL1	Tengo dificultad para controlar la orina	0	1	2	3	4
BL3	Siento ardor/escozor al orinar	0	1	2	3	4
Cx7	Siento molestias al orinar	0	1	2	3	4
HN1	Puedo comer lo que me gusta	0	1	2	3	4

APPENDIX 5 – FIGO STAGING OF CANCER OF THE CERVIX UTERI (2018)

Stage I

The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
IA1 Measured stromal invasion of <3.0 mm in depth
IA2 Measured stromal invasion of ≥3.0 mm and <5.0 mm in depth
IB Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri[b]
IB1 Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2 Invasive carcinoma ≥ 2 cm, and <4 cm in greatest dimension
IB3 Invasive carcinoma ≥ 4 cm

Stage II

The carcinoma invades beyond the uterus, but has not extended to the lower third of the vagina or to the pelvic wall
IIA Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1 Invasive carcinoma <4.0 cm in greatest dimension
IIA2 Invasive carcinoma ≥4.0 cm in greatest dimension
IIB With parametrial involvement but not up to the pelvic wall

Stage III

The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic or para-aortic lymph nodes[c]
IIIA The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
IIIC Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
IIIC1 Pelvic node metastasis only
IIIC2 Para-aortic lymph node metastasis

Stage IV

The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
IVA Spread of the growth to adjacent organs
IVB Spread to distant organs (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)

When in doubt the lower staging should be assigned.

a. Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages.
b. The involvement of vasculat/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered
c. Adding notation of r (imaging) and p (pathology) to indicate findings that are used to allocate the case to Stage IIIC. Example: if imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

APPENDIX 6 – DRUGS WHICH ARE INHIBITORS OF P-GLYCOPROTEINS (FROM FDA DRUG DEVELOPMENT AND DRUG INTERACTIONS)

- Amiodarone (Cordarone®)
- Azithromycin (Zithromax®)
- Captopril (Capoten®)
- Carvedilol (Coreg®)
- Clarithromycin (Biaxin®)
- Conivaptan (Vaprisol®)
- Cyclosporine (Neoral®, Gengraf®, Sandimmune®)
- Diltiazem (Cardizem®, Cartia®, Dilacor®, Diltia®)
- Dronedarone (Multaq®)
- Erythromycin (E.E.S®, Ery-tab®)
- Felodipine (Plendil®)
- Itraconazole (Sporanox®)
- Ketoconazole (Nizoral®)
- Lopinavir and ritonavir (Kaletra®)
- Quercetin (supplement)
- Quinidine
- Ranolazine (Ranexa®)
- Reserpine
- Ritonavir (Norvir®)
- Saquinavir (Invirase®)
- Simeprevir (Olysio®)
- Simvastatin (Zocor®)
- Suvorexant (Belsomra®)
- Tacrolimus (Prograf®)
- Tamoxifen
- Telaprevir (Incivek®)
- Ticagrelor (Brilinta®)
- Verapamil (Calan®,Covera-HS®, Isoptin®, Verelan®)

APPENDIX 7 – ACCEPTABLE CHEMOTHERAPY REGIMENS

1. Cisplatin/paclitaxel/bevacizumab*
2. Carboplatin/paclitaxel/bevacizumab*
3. Cisplatin/paclitaxel
4. Carboplatin/paclitaxel
5. Cisplatin/topotecan
6. Cisplatin
7. Carboplatin

*If bevacizumab given, 6 weeks must elapse between last dose of bevacizumab and first radiation treatment.