Phase 1b/2 trial of preoperative niraparib, dostarlimab, and hypofractionated radiotherapy for the treatment of locally-advanced rectal cancers.

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Protocol version:	Amendment 1 (protocol v.5.0)
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SUMMARY OF CHANGES FROM PREVIOUS VERSION

Affected Section(s)	Summary of Revisions Made	Rationale
01 Jul 2023	**Amendment 1 (protocol version 5)**	
1.1	Inserted "…as part of total neoadjuvant therapy" to phase 1 primary objective	National standard of care changed to adopt total neoadjuvant therapy with surgical indication for those with residual disease burden post-treatment. Delaying or omitting surgery is preferable (when warranted) for patient outcomes and cannot be negated for research purposes. Trial design revised to accommodate this change in standard of care: upfront radiation, followed by FOLFOX chemotherapy, and then evaluation for surgery. Surgery is now medically indicated only, so samples are only obtained if surgery is indicated and performed for treatment.
	Changed "surgical resection" to "FOLFOX chemotherapy" for to phase 1 primary objective	
	Revised primary objective for phase 2 to clinical complete response rate	
	Revised secondary objective from "…until day of surgery," to "start of adjuvant FOLFOX chemotherapy"	
	Revised secondary objective for phase 2 from "complete clinical response rate," to {"organ preservation, clinical pathologic response rate…"	
	Revised study population from hypofractionated with combined chemo to total neoadjuvant therapy upfront with radiation	
	Revised description of study intervention	
	Updated number of subjects needed	Updated power calculations from statistician
1.2	Revised schema description to new treatment paradigm.	As per previous.
1.3	Updated schedule of activities to new treatment paradigm.	As per previous.
2 (throughout)	Updated study rationale to align to findings supporting total neoadjuvant therapy (TNT)	As per previous.
3	Updated objectives and endpoints to align with shift from surgical resection to TNT (which reduces need for surgery post-treatment)	As per previous.
4.1	Updated hypothesis	As per previous.
5.1.1	Updated inclusion criterion 5	As per previous.
5.1.2	Updated exclusion criteria 12 through 14; renumbered appropriately	As per previous.
6.1.2.1.1	Updated dose limiting toxicities to align to new trial design	As per previous.
6.1.2.1.3	Inserted, "with stricter criteria later in treatment (after 8-10 weeks) to minimize the chances of delaying start of chemo because of ongoing cytopenias."	As per previous.
8.1.2	Revised final pathology specimen "as applicable" to accommodate non-mandatory surgery	As per previous.
8.1.3	Updated timeframe to "until the start of FOLFOX chemotherapy"	As per previous.
8.2.4	Revised active follow-up to align to new treatment paradigm	As per previous.
9	Updated throughout for new calculations based upon new treatment paradigm	As per previous.
10.4	Updated to reflect revisions	Housekeeping

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) CODE of Federal Regulations (CFR) applicable to clinical studies (45 CFR §46, 21 CFR §50, 21 CFR §56, 21 CFR §312, and/or 21 CFR §812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

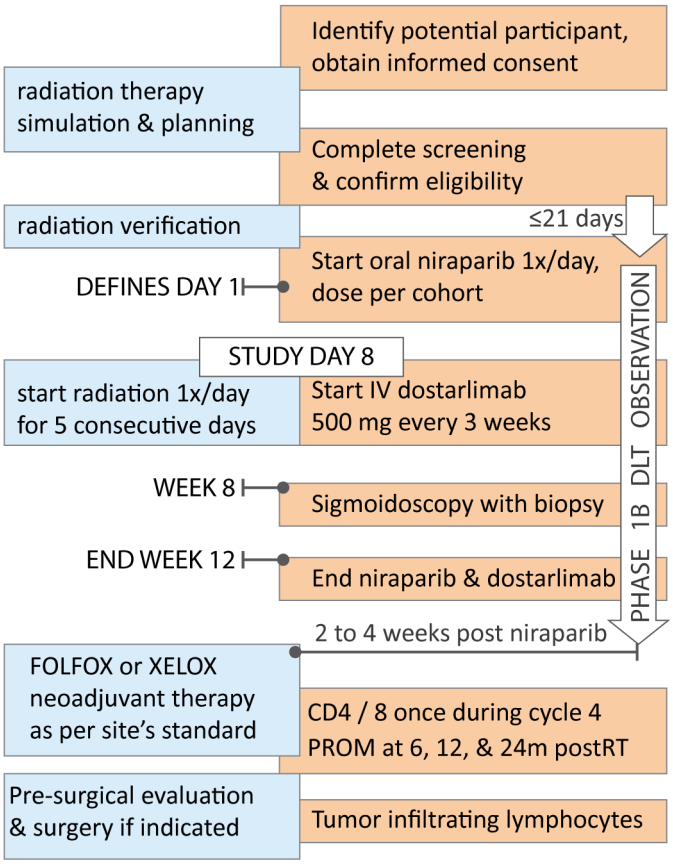
1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Title:	Phase 1b/2 trial of preoperative niraparib, dostarlimab, and hypofractionated radiotherapy for the treatment of locally advanced rectal cancers.
Study Description:	This clinical trial employs a dual phase strategy to determine the maximum tolerated dose of niraparib when combined with dostarlimab and hypofractionated radiation (phase 1) and then testing the recommended phase 2 dose level in an early phase 2 design to identify initial effect size on tumor response as well as patient reported outcome measures.
Phase 1 objective	**Primary objective.** Using a traditional 3+3 cohort design, determine the maximum tolerated niraparib dose for when combined with dostarlimab and hypofractionated radiation as part of total neoadjuvant therapy in patients with locally advanced rectal cancer recommended to receive neoadjuvant chemoradiation therapy and FOLFOX / XELOX chemotherapy.
Phase 2 objectives	**Primary Objective.** Evaluate the clinical complete response rate at surgical evaluation post-neoadjuvant chemotherapy as preliminary evidence of anti-tumor activity of niraparib, dostarlimab, and hypofractionated radiotherapy. **Secondary objective**. Evaluate and characterize adverse events, including hematologic and metabolic toxicities, associated with the combined therapeutic regimen from day 1 of therapy until start of adjuvant FOLFOX or XELOX chemotherapy. Adverse events will be graded using the CTCAE v 5.0. Secondary clinical end points will include organ preservation rate, pathological clinical response rate (in patients with high tumors), progression-free survival, overall survival, metastasis free survival, ostomy free survival, local recurrence free survival, and objective response rates.
Endpoints:	Dose limiting toxicities (DLTs) Adverse events, graded using CTCAE v. 5 Patient reported outcome measures using PROMIS validated questions Tumor measurements, using RECIST v.1.1 Objective response rates, using RECIST v 1.1 Peripheral and Tumor Infiltrating CD4 and CD8 lymphocytes
Study Population:	Patients with locally advanced rectal cancer referred for consideration of total neoadjuvant therapy with upfront radiation
Phase:	1 / 2
Description of Sites Enrolling Participants:	Enrollment will be opened at a single academic site.

Description of Study Intervention:	Administered dose of niraparib is determined by: - Phase 1: assigned cohort and dose limiting toxicities experienced - Phase 2: recommended phase 2 dose (identified in phase 1) Study agents are administered in a combined regimen over 12 weeks: - Oral niraparib (GlaxoSmithKline) - Intravenous dostarlimab (GlaxoSmithKline) Hypofractionated radiation therapy is administered daily during week 2, 5 Gray per fraction for a total of 25 Gy. Niraparib and dostarlimab continue through study week 12. Patients will return to standard of care FOLFOX / XELOX chemotherapy 2-4 weeks after completion of niraparib and dostarlimab. Clinical response assessment with endoscopy and pelvic MRI will occur 4-6 weeks after chemotherapy for pre-surgical evaluation. Recommendation for surgery vs endoscopic surveillance will be left to the treating colorectal surgeon per standard of care guidelines.
Study Duration:	Based upon required sample size (up to 38 subjects), the study is anticipated to complete accrual within 2.5 years.
Participant Duration:	Active study participation lasts up to 3 months.

1.2. SCHEMA



Screening. Physical exam, medical history, recommendation for combined modality therapy, and concomitant medication review

Solicited AEs. Radiation dermatitis, diarrhea, nausea, mucositis, fatigue, and rash.

PROM. Individualized questions based on subject preference and individual risk assessment (e.g. weight loss, fatigue, pain).

Critical endpoints. Tumor infiltrating lymphocytes at W8 and at final pathology specimen (when applicable). Dose limiting toxicities through initiation of FOLFOX/XELOX chemotherapy (≤ study week 18), and pre-surgical evaluation after completion of neo-adjuvant chemotherapy.

End of active participation. Initiation of FOLFOX/XELOX chemotherapy (≤ study week 18), dose limiting toxicity, disease progression, unacceptable event, non-compliance, or withdrawal.

Follow-up. Minimum 2 weeks following completion of experimental therapy.

Selected Patient Eligibility Requirements (Section 5.1 & 5.2)

- Ability to understand and the willingness to sign a written informed consent document
- Willingness to comply with study procedures
- Diagnosis of locally advanced rectal cancer
- Indication for total neoadjuvant therapy with upfront radiation therapy
- ECOG of 0 or 1
- Negative pregnancy test per institutional guidelines
- Agrees to contraception during therapy
- Agrees to adhere to Lifestyle Considerations

1.3. SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screen	Baseline	Active Monitoring Phase				Comments
			Priming	Treatment	Active follow-up[H]	Long-term	
Study Weeks:		≤ 21d	W1	W2-W12	through 24m post RT	24 to 60m postRT	
Informed consent	X						LAR not allowed
Physical exam	X	X	≤ 7d of D1[A,]	prior to each infusion & on last day RT			Dr. Day for RT and *fini*
Pregnancy test	X		≤ 72h of D1	prior to infusion			Per institutional policy
CRT, ALT, AST, TBIL	X						
PT/PTT/INR	X						
CMP, including glucose		X		≤72 h of infusion			
CBC w/diff	X	X	≤ 7d of D1[A]	Weekly	≤7 d of EOT		
Thyroid panel		X	Begin 4 weeks after D1 and then every 6 weeks through EOT visit				TSH, T3 or FT3, and FT4
Urinalysis	X		≤ 7d of D1[A]	prior to infusion			
HBV/HCV	X						
CD4/CD8 lymphocytes[B]		X		W8 & ≤ 7d of last dose	1x during cycle 4[K]		
ECG	X						
Pelvic MRI	X			W8 (±1 week)			
C / A / P CT or PET/CT	X				Chart Review[J]	Chart Review[J]	≤ 3 months of day 1
Tumor biopsy	X			W8 (±1 week)			
Histology	X						
Mutation analysis		C					
Tumor-infiltrating lymphocyte testing		C		W8 (±1 week)	If applicable, at surgery	If applicable at surgery	
Niraparib			orally, once daily, for a maximum of 12 weeks				
Dostarlimab				RT fraction 1 W5, W8, W11			RT starts on a Monday. ± 3 day window
Radiation therapy				D8 – D12			
Scope[D]				W8 (± 1 week)			± 1 week
Vitals (T, HR, BP, wt)[E]	X	X	≤ 7d of D1[A]	Pre/post dostarlimab infusion			Seated position
Adverse events		X	X	D8 & end RT At each infusion			
Concomitant medication review		X		RT day 1 At each infusion			
PRO		X	≤ 7d of D1[A]	At each infusion	6, 12, & 24m postRT		At SOC post-RT visits
EHR/ record review			Medical record reviewed for adverse events through 5 years following radiation therapy				
Assess for MDS/AML[F]			≤ 7d of D1[A]	At each infusion			
Bone marrow aspirate and biopsy[G]			For any patient diagnosed with, or suspected to have, MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist				

A Performed up to 7 calendar days prior to first dose of niraparib. Screening / baseline assessments may be used if compliant with window.

B Can be performed locally but charge test to study. Assessed at baseline, W8, ≤ 7 calendar days of the last dose of niraparib, and W21.

C Exempt from window at specified timepoints.

D Can be anoscopy, sigmoidoscopy, or colonoscopy as per surgical preference.

E Vital signs include: systolic and diastolic blood pressures while the patient is in a seated position, weight, and temperature. Blood pressure and heart rate must be monitored weekly for first 2 months and then monthly during niraparib treatment. Patients may have blood pressure and heart rate monitored at or near home.

F Assessment performed by physician or investigator utilizing CBC with differential; order bone marrow if MDS / AML suspected.

G For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to GSK. A redacted copy of the hematologist's report of aspirate/biopsy findings including a classification according to WHO criteria and other sample testing results related to MDS/AML will be provided to the PI and to GSK.

H End of treatment visit is the end of the dose limiting toxicity window. This window is through study week 16 (4 weeks after the last treatment of niraparib or dostarlimab, whichever is later) **or** at the start of the neoadjuvant chemotherapy (chemo postRT). EOT visit must occur prior to the first dose of chemotherapy.

J Standard of care imaging (CT, PET/CT, MRI) will be obtained and utilized for disease assessment and response outcomes. Frequency of review for imaging is at site discretion but should be at least twice yearly.

K Refers to neoadjuvant chemotherapy cycle (i.e. chemotherapy post radiation).

2. INTRODUCTION

2.1. STUDY RATIONALE

Our preliminary data confirm our central hypothesis that hypofractionated RT and PARP inhibitors can enhance responsiveness to CPIs in both MSS and MSI CRCs and supports the clinical investigation of this promising combination.[1] LARC is the ideal clinical entity in which to test this approach in the definitive (curative) setting for several reasons. First, our preliminary data suggest that enhancement of tumor antigen presentation by PARP inhibitors is specific to higher doses of radiotherapy (> 4 Gy). Conventional preoperative and definitive chemoradiotherapy for most solid-tumors utilizes daily fraction sizes of 1.8-2.0 Gy. In LARC, short-course radiotherapy, which is delivered in 5 fractions of 5 Gy each, is an accepted standard of care that provides equivalent outcomes to conventional long-course chemoradiotherapy in randomized trials of preoperative chemoradiation and total neoadjuvant therapy. Second, short-course radiotherapy in LARC is delivered without concurrent chemotherapy. This simplifies clinical investigation of combination therapies by obviating the need for the inclusion of concurrent standard of care chemotherapies. Third, PARP inhibitors and CPIs have both been tested with concurrent pelvic radiotherapy and demonstrated acceptable toxicity profiles.[2-5] Fourth, LARC is managed with preoperative RT which enables both clinical and pathologic assessment of responses to therapy. Finally, as described below, unlike may cancers, omission of surgery is an acceptable option for LARC patients achieving complete responses to neoadjuvant therapy. Thus, in LARC, clinical and pathologic complete response rates are not only early endpoints that may correlate with long-term clinical outcomes but also a clinically-meaningful endpoint that can lead to the omission of morbid resections resulting in improved QOL for patients and the potential for significant cost-savings.

2.2. BACKGROUND

2.2.1. LOCALLY ADVANCED RECTAL CANCER: AVAILABLE THERAPIES

Until recently, standard of care therapy for locally-advanced rectal cancer (LARC) was preoperative chemoradiotherapy followed by surgical resection and adjuvant chemotherapy.[6] This approach provided local (pelvic) control rates of approximately 90%, long-term cure rates of 65-80%, and pathologic complete response rates (pCR) of approximately 15%.[7,8] While these long-term outcomes are significantly better than surgery alone, trimodality therapy is associated with a number of clinically-significant toxicities that negatively impact quality of life (QOL) for survivors. Some of the most significant toxicities are the result of mesorectal resections. Patients with low tumors involving or closely abutting the anal canal or internal sphincter complex require an abdominal perineal resection (APR) with anal closure and permanent end colostomy. Patients whose tumors are sufficiently distanced from the internal sphincter complex can undergo a low anterior resection (LAR) with coloanal anastomosis and avoid a permanent colostomy. However, most of patients will experience symptoms of LAR syndrome which include abdominal cramping, pain, bloating, diarrhea, fecal urgency, and incontinence.[9,10]

Since up to 15% of patients have no evidence of cancer on final pathology, it was long hypothesized that omission of surgery in patients with apparent complete responses to neoadjuvant chemoradiation may represent a promising way to improve long-term QOL in appropriately selected patients. Multiple prospective and retrospective studies have demonstrated the feasibility of this approach. Depending on the criteria used to define complete response rates (ex, endoscopy alone vs endoscopy plus tumor site biopsy and pelvic MRI), local tumor regrowth rates during surveillance have ranged from 10-30%. Importantly, >90-95% of local regrowth can be salvaged surgically and long-term DFS and OS appear comparable to historic values after immediate surgery. As predicted, non-operative management is also associated with improved bowel function scores and decreased rates of incontinence. The National Comprehensive Cancer Network (NCCN) guidelines now consider non-operative management an acceptable option for patients treated at high volume centers with experienced multidisciplinary teams and its use has greatly increased at major US cancer centers. The current practice within our multidisciplinary oncology group

is to offer non-surgical watch and wait surveillance to most patients with low and mid-rectal tumors who achieve a clinical complete response to neoadjuvant therapy as assessed by both imaging and endoscopy. Surgery is still recommended for patients with tumors involving the high rectum and rectosigmoid junction as there is uncertainty over the distribution of nodal recurrences and appropriateness of non-surgical management in this population. A major clinical focus for LARC has included efforts to improve long-term QOL by obviating the need for surgical resection

In addition to considering non-surgical management in appropriate patients, the recommended sequence of trimodality therapy for LARC has also changed. Looking to improve outcomes further, several prospective studies assessed the feasibility and initial efficacy of total neoadjuvant therapy (TNT) in which patients received 4-8 cycles of chemotherapy in addition to chemoradiation before surgery. Several consistent observations have been made across studies. First, chemotherapy-associated toxicity appears to be lower in the setting of TNT than when given adjuvantly after surgery and receipt of the total number of intended cycles of chemotherapy is higher with TNT. Second, the observed pCR ranges from 20-35% which is roughly double that observed with chemoradiation alone. There is also some randomized evidence that TNT may also improve long-term oncologic outcomes as well. The RAPIDO study randomized patients with LARC to short course radiation (5 Gy x 5) followed by FOLFOX chemo and then surgery or conventional therapy (chemoradiation -> surgery -> chemotherapy) and at 3 years follow up observed a significant reduction in treatment failures (23.7 vs 30.4%) and metastatic progression (20 vs 26.8%) in addition to improved pCR (28 vs 14%). Since TNT appears to be better tolerated and associated with significantly higher pathologic complete responses rates and delayed disease progression, the NCCN Panel now recommends it as the preferred approach for stage II-III LARC. Regarding the sequencing of chemo and radiation within the context of TNT, there is some evidence that upfront chemoradiation may offer several advantages over upfront chemotherapy. The OPRA and CAO/ARO/AIO-12 studies both randomized patients receiving TNT to upfront chemoradiation vs upfront chemotherapy and observed similar long-term disease control with both sequences. However, the pCR (17 vs 25%) and 3-year organ preservation rates (53 vs 41%) were both higher with upfront chemoradiation in the OPRA study. Based on these observations, the NCCN Panel further recommends consideration of upfront radiation followed by chemotherapy particularly in cases where non-surgical management may be considered.

While TNT undoubtedly offers some advantages over conventional therapy, further advances are still needed. Even with TNT, only up to 40% of subjects will achieve a cCR. Further, gains in long-term oncologic outcomes, including PFS and mPFS are modest and there is no evidence of improved OS with TNT. Thus, additional strategies which enhance responses to TNT are needed to further improve early responses (and hence, organ preservation rates) and long-term disease control.

The NRG cooperative group has been testing the addition of radiosensitizers to 5-FU-based chemoradiation as part of TNT in their GI-002 randomized trial.[11] In the first iteration, patients were randomized to 5-FU ± veliparib (a PARP inhibitor) chemoradiotherapy.[3] While the study did not meet its primary end point (improvement in neoadjuvant regression score), the addition of veliparib did provide encouraging results with regards to pCR (21.6 vs 32.8%). In its second iteration, the investigators tested the addition of the PD-1 antibody pembrolizumab to 5-FU chemoradiation.[5] The incidence of any grade 3/4 toxicities was increased in the experimental arm (48.2 vs 37.3%) but there were no significant increases in any individual severe toxicities and the treatment was deemed safe.

The clinical utility of immune check-point inhibitors (CPIs) for tumors other than mismatch repair proficient (pMMR) colorectal cancers (CRC) is currently limited. Elevated tumoral PD-L1 expression may occur in up to 40-60% of CRCs.[12] However, clinical responses to anti-PD-1 monotherapy are poor in patients with metastatic CRC except for the 10-15% who also harbor microsatellite instability (MSI) mutations.[13-15] In contrast to more immunogenic histologies, elevated tumoral expression of PD-L1 is not sufficient to sensitize CRC to CPIs. This suggests that additional mechanisms of resistance to immunotherapy must be overcome in order to utilize these promising therapies in patients with metastatic CRC. Radiation therapy (RT) can overcome resistance to CPIs and enhance local and systemic tumor control in a phenomenon referred to as the abscopal effect. The mechanism of this enhancement involves a combination of pro-inflammatory effects including enhanced MHC-1-mediated tumor antigen presentation, increased tumor infiltration by activated CD8+ T-cells, and decreased local concentrations of immunosuppressive

cell populations.[16-19] RT also modulates the PD-L1 axis by increasing PD-L1 expression through the CHK1/STAT1/3 pathway in response to the generation of DNA double-strand breaks further supporting the rationale for combination of RT and CPI therapy.[20,21] Several classes of small molecule drugs, including inhibitors of PARP and HDACs, can also enhance systemic responsiveness to CPIs.[22-24] PARP inhibition leads to the accumulation of cytosolic DNA and stimulation of cGAS/STING-mediated type-1 interferon signaling. PARP inhibition can also increase PD-L1 levels via ATM/GSK3β signaling to enhance α-PD-1-mediated clearance of poorly immunogenic murine tumor models. These preclinical studies provide a mechanistic basis to predict possible synergy between PARP inhibitors and CPIs. The clinical relevance of these findings is supported by encouraging results of two recent early-phase clinical investigations of the PARP inhibitor niraparib in combination with pembrolizumab in poorly immunogenic ovarian and triple negative breast cancers.[25,26] Vinayak et al.[26] observed a 49% disease control rate among 55 women with advanced triple negative breast cancer who had failed at least one prior line of chemotherapy. Platinum resistant ovarian cancers are generally aggressive tumors with limited treatment options and Konstantinopoulos et al.[25] noted very encouraging disease control rate (65%) with niraparib + pembrolizumab therapy in a phase 1/2 trial of 67 patients with platinum resistant tumors. Importantly, PARP inhibitors are also potent radiosensitizers that can enhance the damaging effects of RT in the tumor microenvironment (TME).[27,28] We hypothesized that the combination of PARP inhibitors and hypofractionated RT would modulate tumor cells to a pro-inflammatory phenotype and enhance responsiveness to CPIs in syngeneic for CRC tumor models.

2.2.2. PRELIMINARY DATA

We utilized two murine syngeneic models of CRC cancer, CT26 and MC38, which represent validated models of MSS and MSI CRC, respectively. We first performed a candidate drug screen ± radiation and identified veliparib as a potent radiosensitizer in MC38 and CT26 murine colorectal tumor cells. We then tested the hypothesis that veliparib pretreatment would enhance MHC-1 antigen presentation by assessing MCH-1 surface localization 24 hours after a single fraction of *in vitro* radiotherapy (2-8 Gy) using flow cytometry. We found that radiation dose-dependently increased MCH-1 surface localization in both cell lines and that veliparib pretreatment significantly enhanced this with high (4-8 Gy) but not lower doses of radiation. We then showed that enhanced MHC-1 surface localization was not mediated by increased expression of antigen processing proteins including MHC-1 (H2-D subunit), TAP-1, or β-2 macroglobulin in either cell line. Previous studies have found that veliparib can enhance delayed expression of inflammatory cytokines following high-dose radiation in highly immunogenic cell lines. We examined the expression of INF-β, CXCL10, IL-6 and the immunosuppressive cytokine TGF-β 1,3, and 7 days after a single fraction of radiation (8 Gy) ± veliparib pretreatment. At 24 hours, radiation increased expression of INF-β and CXCL10 in both cell lines and this was not significantly altered with veliparib pretreatment. However, INF-β and CXCL10 expression was markedly increased 3 and 7 days after radiation in MC38 and CT26 cells (respectively). Veliparib pretreatment significantly increased delayed expression of INF-β in both lines and CXCL10 in CT26 cells. Importantly, veliparib did not increase expression of TGF-β at any time point in either cell line. We also assessed the effects of veliparib and radiation on the surface localization of the immune-modulating proteins PD-L1 and calreticulin. Radiation significantly increased surface localization of PD-L1 at 24 hours and this was significantly increased by veliparib pretreatment. There was a strong trend towards increased surface localization of calreticulin, but this did not reach statistical significance.

Collectively, our *in vitro* studies demonstrate that veliparib and high-dose radiation induce a number of changes in tumor cells that could render them more susceptible to immune recognition and clearance; particularly when combined with anti-PD-1 therapies. We tested this hypothesis by assessing *in vivo* tumor growth delay/rejection and survival using unilateral flank tumor models. To our knowledge, the combination of veliparib, hypofractionated radiation, and α-PD-1 antibodies had not been previously tested and the optimal sequencing of therapies was unknown. We performed a pilot study in which we tested the effect of sequencing of treatments on tumor growth delay in animals with MC38 flank tumors. We observed very high rates of local tumor control regardless of how therapies were sequenced. We then proceeded with a definitive experiment. BALB-C and C57bl/6 mice were inoculated with unilateral CT26 or MC38 (respectively) flank tumors. Once tumors were established (approximately 500 mm^3), animals were treated with sub-ablative radiotherapy (8 Gy x 2 over 3 days), veliparib (25 mg/kg BID x 7

days), an anti-PD-1 antibody (clone RMP 1-14, 100 mg/kg x 3 over 6 days), or combinations of the above treatments. As expected, CT26 tumors were resistant to α-PD-1 therapy. The combination of veliparib + RT + α-PD-1 antibodies delayed tumor growth significantly longer than all other treatments. However, this was largely a transient delay as only 1/11 mice achieved complete tumor regression. In contrast, MC38 tumors were more sensitive to α-PD-1 treatment. Radiation + veliparib and radiation + α-PD-1 antibodies both delayed tumor growth longer than radiation alone and 2/7 mice treated with radiation + α-PD-1 antibodies achieved complete tumor regression. Triple therapy with radiation + veliparib + α-PD-1 antibodies stimulated significantly greater tumor growth delay and overall survival than all other treatments and complete rejection of 8/10 tumors. We further demonstrated that the concurrent administration of radiation and α-PD-1 antibodies is required for maximal therapeutic efficacy as complete responses were only observed in 4/10 mice in which the administration of α-PD-1 antibodies was delayed for 7 days after completion of radiation. Finally, we confirmed that synergy between RT and α-PD-1 therapy ± veliparib is immune-mediated using T-cell depletion studies. Our studies provide preclinical evidence that concurrent radiation and PARP inhibition can enhance CPI-mediated tumor clearance in syngeneic rectal cancer models and support the clinical investigation of combination therapy with radiation, PARP inhibition, and CPIs as a promising therapeutic approach to locally advanced rectal cancers.

2.2.3. CLINICAL EXPERIENCE OF RADIATION WITH PARP INHIBITORS AND CPIS

To date, no results have been reported regarding the safety of the combination of radiation + PARP inhibitors + CPIs. However, the combinations of pelvic radiation + PARP inhibition, pelvic radiation + CPIs, and PARP inhibitors + CPIs have been reported and all appear to be well tolerated with relatively low risks of severe toxicity. The NRG GI002 cooperative trial randomized 178 patients with locally advanced rectal cancer to neoadjuvant FOLFOX chemotherapy followed by FU-based chemoradiation (50.4 Gy in 28 fractions) ± the PARP inhibitor veliparib and surgical resection.[11] While it did not reach statistical significance, they observed a strong trend towards higher pCR with veliparib (33.8 vs 21.6%, P=0.14) without any significant increases in grade ≥ toxicity compared to standard chemoradiation.[3] In the second iteration of the trial the randomization was FU-based chemoradiation ± pembrolizumab. The incidence of any grade 3/4 Aes was slightly increased in the pembrolizumab arm (48.2 vs 37.3%) but there were no significant increases in any specific toxicities and the treatment was deemed safe.[5] Safety data has also been presented for patients with bladder or cervical cancers receiving concurrent pelvic radiation + CPIs. The DUART phase 1/2 trial treated 26 platinum ineligible patients with muscle invasive bladder cancer with pelvic radiation (64.8 Gy in 36 fractions) + concurrent durvalumab.[4] Grade 3 cystitis was only observed in 3 (11.5%) of patients which is comparable to or lower than historic rates observed with conventional chemoradiation.[29-31] Duska et al.[2] also recently presented the initial safety data of a phase 1/2 study in which patients with locally advanced cervical cancer were randomized to SOC chemoradiation (45 Gy whole pelvis followed by 30 Gy HDR brachytherapy boost with concurrent cisplatin) + concurrent or adjuvant pembrolizumab. Severe toxicity was low in both arms. Only 2/52 patients experienced acute grade 3 GI toxicity (which is the most common acute toxicity associated with pelvic radiation) which again is comparable to historic results with SOC chemoradiation. It is worth noting that the total radiation dose used for bladder and cervical cancer is significantly higher than for preoperative rectal cancer. Assuming an α/β of 3 (an accepted standard for the rectum and bladder) the equivalent dose (EQD2) for rectal, bladder, and cervical cancer are 40, 64, and 98 Gy respectively. Only one study has noted unexpected toxicity with pelvic radiation and concurrent CPI. The phase 1 PLUMMB trial of aggressively hypofractionated radiation (36 Gy in 6 fractions) and pembrolizumab (NCT02560636) for metastatic or advanced bladder cancer which was discontinued because 3 of the first 5 patients enrolled experienced grade 3 cystitis. [32,33] It is noteworthy that this trial has since reopened at a similar radiation dose to that proposed in our study (24 Gy in 6 fractions). Two phase 1/2 trials have also reported safety with concurrent niraparib and pembrolizumab (without radiation) in patients with triple negative breast cancer or platinum resistant ovarian cancer and neither study observed any evidence of increased hematologic toxicity or immune-related side effects.[25,26] Collectively, the existing literature largely suggests that combinations of PARP inhibition, CPI, and radiation are generally well tolerated with comparable rates of severe toxicity to SOC chemoradiation.

2.3. RISK/BENEFIT ASSESSMENT

2.3.1. KNOWN POTENTIAL RISKS

The following risks are known to occur based on the U.S. prescribing information and/or current Investigators' Brochure from clinical trials to date.

2.3.1.1. NIRAPARIB

The following adverse events are linked to administration of niraparib occur based on the U.S. prescribing information and/or current Investigators' Brochure from clinical trials to date.

- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) (0.8% incidence)
- Platelet count decreased, grade ≥3: 39%
- Anemia, grade ≥3: 31%
- Neutrophil count decreased, grade ≥3: 21%
- Hypertension, grade 3 or 4: 5-9%. Hypertensive crisis has also been reported.
- Nausea, any grade: 65%
- Platelet count decreased, any grade: 60%
- Anemia, any grade: 56%
- Fatigue, any grade: 55%
- Constipation, any grade: 39%
- Musculoskeletal pain, any grade: 36%
- Abdominal pain, any grade: 35%
- Vomiting, any grade: 33%
- Neutrophil count decreased, any grade: 31%
- Anorexia, any grade: 24%
- White blood cell decreased, any grade: 24%
- Insomnia, any grade: 23%
- headache, any grade: 23%
- dyspnea, any grade: 22%
- rash, any grade: 21%
- diarrhea, any grade: 18%
- hypertension, any grade: 17%
- cough, any grade: 16%
- dizziness, any grade: 14%
- acute kidney injury, any grade: 13%
- urinary tract infection, any grade: 12%
- hypomagnesemia, any grade: 11%

2.3.1.2. DOSTARLIMAB

The following adverse events are linked to administration of dostarlimab monotherapy occur based on the current Investigators' Brochure from clinical trials to date

- Anemia, ≥3: 1.7%
- Fatigue, ≥3: 1.7%
- Alanine aminotransferase increased, ≥3: 1.1%
- Lipase increased, ≥3: 1.1%

- Aspartate aminotransferase increased, ≥3: 0.9%
- Diarrhea, ≥3: 0.9%
- Adrenal insufficiency, ≥3: 0.6%
- Amylase increased, ≥3: 0.6%
- Hyperglycemia, ≥3: 0.6%
- Nausea, ≥3: 0.6%
- Rash, ≥3: 0.6%
- Asthenia, ≥3: 0.4%
- Alkaline phosphatase increased, ≥3: 0.4%
- Colitis, ≥3: 0.4%
- Constipation, ≥3: 0.4%
- Anorexia, ≥3: 0.4%
- Hyperlipidemia, ≥3: 0.4%
- Hypotension, ≥3: 0.4%
- Neutrophil count decreased, ≥3: 0.4%
- Pneumonitis, ≥3: 0.4%

2.3.1.3. NIRAPARIB COMBINED WITH DOSTARLIMAB

The following adverse events are linked to combination therapy of niraparib and dostarlimab based on the current Investigators' Brochure from clinical trials to date.

Table 2.3.1.3. Summary of treatment emergent adverse events ≥ 10% of subjects receiving dostarlimab-combination therapy (safety population). Reported as percentage of total subjects (n=96).§

CTCAE term	Reported	Related	grade ≥ 3
Fatigue	49	19.8	8.3
Nausea	52.1	12.5	5.2
Anorexia	22.9	3.1	0
Constipation	34.4	8.3	3.1
Dyspnea	21.9	3.1	1.0
Vomiting	37.5	7.3	4.2
Anemia	30.2	3.1	13.5
Diarrhea	21.9	7.3	2.1
Cough	14.6	6.3	0
Hypertension	35.4	4.2	13.5
Abdominal pain	18.8	0	3.1
Edema (peripheral)	12.5	1.0	0
Arthralgia	10.4	3.1	1.0
Headache	24.0	3.1	2.1
Insomnia	21.9	1.0	0
Pyrexia	11.5	3.1	1.0
Dehydration	7.3	0	0
Rash	18.8	14.6	2.1
Hyponatremia	22.9	5.2	9.4
Pruritus	8.3	7.3	0
Weight loss	12.5	1.0	0

§ Source: Dostarlimab Investigator's Brochure, edition 5.0 (24 March 2020).

2.3.1.4. HYPOFRACTIONATED RADIATION THERAPY

Short course hypofractionated radiotherapy is an accepted standard of care that is typically delivered without concurrent chemotherapy. In the context of TNT, short course radiotherapy appears to be as effective as long course chemoradiation. In the RAPIDO study, the pCR after short course radiation followed by chemotherapy was 27% which is equivalent to that observed TNT studies using long course chemoradiation such as GI001 (24%). The most common toxicities include GI (diarrhea, nausea, mucositis) and GU (dysuria and cystitis) toxicities which result from inclusion of portions of the rectum, bladder, and small bowel in the radiation field. These tend to be self-limited and rarely cause delays with planned surgery or adjuvant chemotherapy.

The acute toxicities most commonly associated with hypofractionated pelvic radiation for rectal cancer38-41 are:

- Diarrhea (any grade): 65%
- Increased urinary frequency/urgency: 35%
- Nausea (any grade): 28%
- Diarrhea > grade 3: 27%
- Dermatitis (any grade): 25%
- Fatigue (any grade): 25%
- Any rectal bleeding: 18%
- Dysuria (any grade): 15%
- Vomiting (any grade): 12%
- Post-surgical anastomotic leak: 11%
- RBCs decreased from baseline: 10%
- Constipation: 10%
- Thrombocytopenia (any grade): 9%
- Acute urinary tract infection: 8%
- Nausea > grade 3: 6%
- Hematuria (any grade): 5%
- Vomiting > grade 3: 2%
- Neutropenia (any grade): < 1%
- Any hematologic toxicity > grade 3: <1%
- Bowel perforation: <1%
- Bladder hemorrhage: <1%

PARP inhibitors and CPIs have been given concurrent with pelvic radiation in previous trials with only modest increases in acute radiation toxicities noted though no data is available with all 3 given concurrently for preop rectal cancer.

In general, there are 2 primary concerns with novel **neoadjuvant** regimens: 1) experimental therapy could delay or preclude curative surgery as prescribed or 2) experimental therapy could increase postoperative morbidity and/or impair long-term rectal function.

One of the most common acute toxicities of niraparib is thrombocytopenia. The possibility that this may be increased with concurrent radiation and dostarlimab cannot be ruled out. Severe (grade ≥ 3) thrombocytopenia is much more common at the 300 mg dosing than 200 mg dosing and largely resolves by 12 weeks even at the higher dose level. This protocol has taken several precautions to minimize the probability of severe thrombocytopenia (or other cytopenias) that could impact receipt of surgery (if indicated). First, the maximal planned niraparib dose is 200 mg (as opposed to 300 mg as a monotherapy). Second, surgery will be delayed for a minimum of 2-5 months after receipt of niraparib while patients receive neoadjuvant chemotherapy. Since niraparib-induced thrombocytopenia typically resolves within 12 weeks, any direct effects of niraparib on platelet counts are expected to resolve before surgery is planned. We will also be checking weekly CBCs and have included specific guidelines related to niraparib dose

reduction or discontinuation as part of the protocol. Additionally, we will utilize IMRT to minimize pelvic bone marrow radiation dosing to try to minimize the risk for significant interaction between niraparib and radiation.

2.3.1.5. ACUTE CYSTITIS IS GENERAL MILD WITH PELVIC RADIATION FOR RECTAL CANCER WITH GRADE 3+ CYSTITIS OCCURRING IN <5% OF PATIENTS. ONLY THE POSTERIOR BLADDER WALL (APPROXIMATELY POSTERIOR 1 CM) RECEIVES PRESCRIPTION DOSE RADIATION IN TREATMENT FOR RECTAL CANCER. GRADE 3+ CYSTITIS IS MORE COMMON WHEN THE ENTIRE BLADDER IS INCLUDED IN THE RADIATION FIELD WITH APPROXIMATELY 10-15% OF BLADDER CANCER PATIENTS BEING AFFECTED. A SINGLE PHASE 1 STUDY THAT DELIVERED HIGH DOSES PER FRACTION (30 GY IN 5 FRACTIONS) TO THE ENTIRE BLADDER FOR INVASIVE UROTHELIAL TUMORS WITH CONCURRENT PEMBROLIZUMAB CLOSED EARLY BECAUSE OF UNEXPECTED (3/5) RATES OF GRADE 3+ CYSTITIS. THE RISK OF GRADE 3 OR HIGHER CYSTITIS SHOULD BE SIGNIFICANTLY LOWER IN OUR TRIAL BECAUSE WE WILL BE USING IMRT TO SPARE MOST OF THE BLADDER FROM HIGH DOSE RADIATION. AT LEAST ONE COMPLETED PHASE 1 STUDY USING A COMBINATION OF EXTERNAL BEAM RADIATION (45 GY IN 25 FRACTIONS) AND AN HDR BRACHYTHERAPY BOOST (30 GY IN 5 FRACTIONS) WITH CONCURRENT CISPLATIN AND PEMBROLIZUMAB HAS SUGGESTED THAT HIGH DOSE RADIATION TO SMALL VOLUMES OF THE BLADDER WITH CONCURRENT IMMUNOTHERAPY IS NOT ASSOCIATED WITH AN INCREASED RISK OF SEVERE CYSTITIS. FOLFOX CHEMOTHERAPY AND TOTAL NEOADJUVANT THERAPY (TNT)

FOLFOX chemotherapy (5-FU, Leucovorin, oxaliplatin) is the most common adjuvant or neoadjuvant used for patients with LARC. FOLFOX is administered by IV infusion on a 2-week schedule. Compared to many chemotherapy regimens, it is generally well tolerated with common side effects including acute cytopenias, gastrointestinal toxicity, and peripheral neuropathy. Pelvic radiation causes many similar side effects and in the setting of TNT it can be difficult to confidently attribute specific toxicities to one treatment or the other depending on the specific sequencing of therapy. As in our study, 460 subjects in the RAPIDO study received short course radiation followed by FOLFOX chemotherapy. The most common acute toxicities noted during chemotherapy in that study included:

- Peripheral Neuropathy (any grade): 84%
- Fatigue (any grade): 68%
- Any hematological toxicity > grade 3: 29%
- Hand-foot syndrome (any grade): 31%
- Abdominal Pain (any grade): 52%
- Rectal Bleeding (any grade): 23%
- Diarrhea > grade 3: 17%
- Oral Mucositis (any grade): 13%
- Proctitis (any grade): 11%
- Cystitis (any grade): 9%
- Fecal Incontinence (any grade): 8%
- Vomiting > grade 3: 2%
- Alopecia (any grade): 2%
- Febrile Neutropenia > grade 3: 1%

Receipt of chemotherapy will not occur during active study participation. Rather, patients will return to standard of care during chemotherapy. As such, dose modifications and treatment holds will be left to the discretion of the treating oncologist following standard of care guidelines and not protocol specified. However, the overlap between

expected toxicities from radiation, experimental therapy, and chemotherapy presents several important considerations. First, unresolved toxicities from radiation, niraparib, and/or dostarlimab (including diarrhea, colitis, or cytopenias) could cause a prolonged delay in starting chemotherapy. While the effect of delaying chemotherapy during TNT on treatment efficacy is unknown, prolonged treatment breaks are typically avoided since theoretically they could enable tumor repopulation and decrease treatment efficacy. Current guidelines recommend delaying chemotherapy for 2-4 weeks after completing radiation to allow adequate resolution of overlapping toxicities. Our trial will recommend the same washout period after completion of experimental therapy. Delays in starting chemotherapy > 4 weeks because of toxicities possibly or definitely related to radiation, dostarlimab, or niraparib will be considered a DLT during phase 1. Second, it is unknown if receipt of radiation, niraparib, and dostarlimab before chemotherapy will increase the incidence or severity of acute toxicities during chemotherapy. Patient charts will be reviewed for toxicities of interest during chemotherapy to ensure that the incidence of severe toxicities does not appear higher than expected based on historic controls.

2.3.2. KNOWN POTENTIAL BENEFITS

Benefit to society:

- The combined therapy could serve as superior antineoplastic regimen compared to standard therapy increasing tumor cell killing, improving resistance to single chemotherapeutic agent and overall survival.
- The combined therapy could improve quality of life for patients who require antineoplastic therapy.

2.3.3. ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Antineoplastic therapy continues to evolve. Evaluating new therapeutic regimens will never be without risk. This phase 1 study will be closely monitored for adverse events, dose limiting toxicities (DLTs), and any conferred benefit. Initial clinical work suggests a benefit compared to standard therapy. The next step in clinical evaluation requires subjects to assume a risk to identify the maximum tolerated dose of the combined regimen. To assess and minimize risks:

- monitoring serum chemistries (including glucose) and cell counts
- scheduled doctor’s appointments and meetings with the research nurses
- 24 hour access to medical personnel through nuclear medicine on-call and radiation oncology on-call
- reviewing all side effects in a timely and efficient manner
- utilizing concomitant medications appropriately to reduce symptoms and side effects
- securing protocol compliance
- discontinuing drug as per stopping rules

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoint	Justification
Primary		
[**phase 1b**] Confirm safety while evaluating niraparib tolerance when combined with dostarlimab and radiation therapy for locally advanced rectal cancer.	Dose limiting toxicity	• A traditional rule based 3+3 design will evaluate the combination treatment using pre-defined dose-limiting toxicities. • DLT assessments using CTCAE v5 will be used to determine recommended phase 2 dose.
[**phase 2**] Determine the anti-tumoral activity or niraparib, dostarlimab, and hypofractionated radiotherapy for locally advanced rectal cancer.	Clinical complete response (cCR) at pre-operative assessment	• Effect on tumor attributable to intervention, not natural history[34] • Based on objective and quantitative assessments including radiologic and endoscopic assessments • This endpoint is clinically important as patients meeting this criterion are potentially eligible for non-surgical watch and wait management by SOC consensus guidelines
Secondary		
Determine pathologic complete response rate (pCR) in patients with locally advanced rectal cancer involving the high rectum recommended to undergo surgical resection regardless of response to neoadjuvant therapy.	Defined as absence of viable tumor in the primary tumor bed and all regional nodes.	• Effect on tumor attributable to intervention, not natural history[34] • Based on objective pathologic variables that strongly correlate with long-term disease control.
Determine organ preservation rate following completion of niraparib, dostarlimab, hypofractionated radiotherapy, and neoadjuvant FOLFOX chemotherapy.	Organ preservation, defined as day 1 therapy to receipt of rectal resection (APR or LAR) for any reason.	• Clinically meaningful endpoint • Impacts patient quality of life and functional status • Treatments have been approved based upon delaying time to salvage surgeries[34]
Determine overall survival in patients with locally advanced rectal cancer when treated with niraparib, dostarlimab, and hypofractionated radiotherapy.	Overall survival, defined as day 1 therapy to death from any cause.	• The hypothesized result is an increase in overall survival, regardless of salvage therapy. • Overall survival is considered the most reliable cancer endpoint.[34] • Overall survival is without bias as an endpoint of therapeutic efficacy.[34]
Determine progression free survival (as per RECIST 1.1) in patients with locally advanced rectal cancer when treated with niraparib, dostarlimab, and hypofractionated radiotherapy.	Progression free survival, defined as day 1 therapy to disease progression or death from any cause. Progression is defined per RECIST 1.1. (radiographic or endoscopic).	• Assessed earlier with smaller sample size compared to OS.[34] • Includes stable disease (compared to ORR) and death (compared to time to progression) • Susceptible to assessment bias in open-label studies. [34] • May not always correlate with survival

Objective	Endpoint	Justification
Determine metastasis free survival (as per RECIST 1.1) in patients with locally advanced rectal cancer when treated with niraparib, dostarlimab, and hypofractionated radiotherapy.	Metastasis free survival, defined as day 1 therapy to disease progression outside of the pelvis or death from any cause. Progression is defined per RECIST 1.1. (radiographic). Equivocal findings on imaging require pathologic confirmation with tissue biopsy.	• Assessed earlier with smaller sample size compared to OS.[34] • Susceptible to assessment bias in open-label studies. [34] • May not always correlate with survival
Determine local recurrence free survival (as per RECIST 1.1) in patients with locally advanced rectal cancer when treated with niraparib, dostarlimab, and hypofractionated radiotherapy.	Local recurrence free survival, defined as day 1 therapy to disease progression within the pelvis or death from any cause. Progression is defined per RECIST 1.1. (radiographic or endoscopic).	• Assessed earlier with smaller sample size compared to OS.[34] • Susceptible to assessment bias in open-label studies. [34] • May not always correlate with survival
Determine ostomy free survival in patients with locally advanced rectal cancer when treated with niraparib, dostarlimab, and hypofractionated radiotherapy.	Ostomy free survival, defined as day 1 therapy to receipt of permanent ostomy (includes colostomy or end ileostomy) or death from any cause. Receipt of a temporary diverting ostomy is not included as an event.	• Assessed earlier with smaller sample size compared to OS.[34] • May not always correlate with survival
Determine objective response rate (as per RECIST 1.1) in patients with locally advanced rectal cancer when treated with niraparib, dostarlimab, and hypofractionated radiotherapy.	RECIST disease response (CR, PR) at 3 months post-radiation. (Stable disease is not considered a component of the RECIST objective response rate, because it can reflect natural disease history rather than a direct therapeutic effect).	• Considered to measure an effect attributable to the drug and not natural history of the disease.[34] • Objective response rate is considered appropriate for accelerated or regular drug approval and is approved by FDA for single-arm studies with smaller sample sizes.
Exploratory		
Explore the patient experience using patient-reported symptoms for patients with locally advanced rectal cancer when treated with niraparib, dostarlimab, and hypofractionated radiotherapy.	Patient reported outcome measures (PROM)	• Initial step in determining impact in holistic health for patients undergoing combined therapy for locally advanced rectal cancer.[34]
Assess changes in tumor infiltrating CD8 and CD4 T lymphocytes following treatment with niraparib, dostarlimab, and hypofractionated radiation	Tumor CD8 and CD4 immunohistochemistry at baseline and 6 weeks post radiation as well as from final pathology specimens as applicable.	• Hypothesized result is that CD8 and CD4 density in tumors is increased following treatment compared to baseline • This exploratory endpoint could provide mechanistic evidence that combination therapy enhances tumor immune infiltration

Objective	Endpoint	Justification
Assess changes in peripheral CD8 and CD4 T lymphocytes following treatment with niraparib, dostarlimab, and hypofractionated radiation	Peripheral CD8 and CD4 lymphocyte count (naïve and activated) at baseline, 6, 12, and 19 weeks post radiation	• Hypothesized result is ratio of activated to naïve CD4 and CD8 lymphocytes is increased following treatment compared to baseline • This exploratory endpoint could provide mechanistic evidence that combination therapy enhances expansion of activated lymphocytes

4. STUDY DESIGN

4.1. OVERALL DESIGN

Hypothesis
Hypofractioned radiation therapy, combined with PARP inhibitors and CPIs, as part of total neoadjuvant therapy (TNT), will enhance therapeutic response compared to standard of care alone (i.e., total neoadjuvant therapy).

Phase
Phase 1b design with an expansion to early phase 2 (phase 1 / 2).

Description of trial
Single site, non-randomized, open-label clinical trial employing convenience-based sampling evaluating up to 41 participants across both phases.

Methods to minimize bias
The following strategies are employed to minimize bias:

- All patients referred for radiation treatment for locally advanced rectal cancers are screened against eligibility.
- Subject eligibility is reviewed by an independent data and safety monitoring committee.
- Adverse events and dose limiting toxicities are reviewed by an independent data and safety monitoring committee.
- Radiologic evaluations for RECIST will be performed with a blinded evaluator.

Dose escalation
Described in section 6.1.2, *dosing and administration.*

Study groups and arms
The phase 1 assessment evaluates 2 cohorts for niraparib while maintaining the same dose and frequency for both dostarlimab and radiation therapy through 12 weeks of niraparib/dostarlimab therapy. The phase 2 assessment is a single experimental arm employing the recommended phase 2 dose for niraparib.

Intervention

- Niraparib (GlaxoSmithKline), daily, for up to 12 weeks.
- Dostarlimab (GlaxoSmithKline), every 3 weeks for a total of 4 administrations over 12 weeks.

Interim analysis
A cohort-based interim analysis for dose-limiting toxicities will be performed after the dose limiting toxicity window for the last cohort-enrollment. Additionally, an overall interim analysis for dose limiting toxicities will be performed prior to the phase 2 expansion to confirm the recommended phase 2 dose.

Stratifications
None.

Sub-studies and/or sub-analyses
None.

4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

Phase 1b. The study design is traditional 3 + 3 with rule escalation. Dose cohorts are based upon Niraparib's prior clinical trials and supported by the prescribing information.

A non-randomized phase 2 expansion is selected due to the early stage of therapy exploration.

4.3. JUSTIFICATION FOR DOSE

The FDA approved dosage for niraparib is between 200 mg to 300 mg (dependent upon patient weight and platelet function) when administered as a monotherapy. To evaluate toxicity of a multimodal oncologic therapy, niraparib will be started at 1/3 of the FDA approved dose. Many radiosensitizers are prescribed at doses considered subtherapeutic as a monotherapy when given concurrent with radiation as lower doses are often enough to induce radiosensitization while minimizing toxicity. PARP inhibitors are potent radiosensitizers and it is highly likely that significant radiosensitization may be achieved using doses that are considered subtherapeutic as a monotherapy. Concurrent PARP inhibition has the potential to increase acute GI/GU toxicity and thrombocytopenia and it is currently unknown how concurrent radiation and CPI may increase this risk.

To evaluate toxicity of a multimodal oncologic therapy, niraparib will be started at 1/3 of the FDA approved dose. Dostarlimab has a standard dosing regimen as provided by the manufacturer (GSK) when combined with niraparib. We are not proposing any dose decreases for dostarlimab as dose adjustments are typically not necessary for CPIs with concurrent radiotherapy. The primary DLTs for CPIs are immune related toxicity and do not appear to increase in frequency with concurrent radiation.

4.4. END OF STUDY DEFINITION

A subject is considered to have completed the study if one of the following has been met:

- The subject has completed interventions and visits as described in the schedule of activities (section 1.2),
- The subject has withdrawn or been withdrawn from further intervention and has completed the necessary follow-up as prescribed (section 7),
- The study has been terminated and the subject has completed the necessary interventions as indicated by the study sponsor.

If a subject has withdrawn or been withdrawn, the subject must provide consent to continue to undergo study assessments (even if the subject is withdrawn/withdraws due to an adverse event). This must be documented in the study chart. If a subject declines further follow-up or assessment, per OHRP/DHHS and FDA guidance, no further interaction may take place with the subject in regard to the study.

5. STUDY POPULATION

5.1. ELIGIBILITY CRITERIA

5.1.1. INCLUSION CRITERIA

1. Ability to understand and willingness to provide informed consent; legally authorized representative will not be utilized compliant with the principles of good clinical practice (i.e., ICH E6(R2)).
2. Stated willingness to comply with all study procedures and availability for duration of study
3. Aged ≥ 18 years at the time of study drug administration
4. Resectable locally advanced rectal cancer (i.e., T3 to T4 or T1-T4 with N1-2 M0).
5. Recommended to receive total neoadjuvant therapy consisting of preoperative radiation therapy followed by systemic FOLFOX chemotherapy
6. Adequate performance status (ECOG of 0 or 1; or KPS of ≥ 70).
7. Agreement to adhere to Lifestyle Considerations (see section 5.2) throughout study duration
8. Participant must agree to not donate blood during the study or for 90 days after the last dose of study treatment.

5.1.2. EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Absolute neutrophil count < 1,500 cells /µL
2. Platelets < 100,000 cells/µL
3. Hemoglobin <9 g/dL
4. Serum creatinine > 1.5 x upper limit of normal (ULN) ***or*** calculated creatinine clearance 60mL/min using the Cockcroft-Gault equation
5. Total bilirubin > 1.5 x ULN (>2.0 x ULN in patients with known Gilberts syndrome) ***or*** direct bilirubin > 1 x ULN
6. Aspartate aminotransferase and alanine aminotransferase > 2.5 x ULN
7. International normalized ratio (INR) or prothrombin time (PT) >1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or partial thromboplastin (PTT) is within therapeutic range of intended use of anticoagulants. Activated partial thromboplastin time (aPTT) >1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
8. Uncontrolled arterial hypertension, i.e. systolic BP > 140 mmHg, diastolic BP > 90 mmHg.
9. Platelet transfusion ≤ 4 weeks prior to initiating protocol therapy. Because chronic low-volume blood loss is a common presentation for colorectal tumors, a single RBC infusion is allowed to correct for Hb <9.0 as long as Hb ≥ 9.0 is maintained until initiation of experimental therapy (with a minimum of 7 days between transfusion and initiation of therapy).
10. Presence of any M1 metastatic lesions. Equivocal liver lesions noted on CT must be worked up further with US or MRI to exclude hepatic metastases prior to enrollment. Suspected metastatic involvement of lymph nodes superior to conventional pelvic radiotherapy fields (the L5/S1 interspace) or in the inguinal canal (inferior to the cranial extent of the femoral heads) on appropriate imaging studies (CT, PET-CT, or MRI) will be considered non-regional metastatic disease for the purposes of this study.
11. Receipt of prior pelvic radiotherapy
12. Known diagnosis of dihydropyrimidine dehydrogenase (DPD) deficiency which is associated with increased risk of severe toxicity to fluoropyrimidine chemotherapy. Owing to its low frequency and high number of mutations of unknown significance, current US practice guidelines do not recommend routine screening for DPD deficiency. Accordingly, screening for DPD deficiency is not required to determine eligibility.
13. Recommended to receive systemic chemotherapy prior to receipt of radiotherapy.
14. Recommended to receive a chemotherapy regimen other than FOLFOX chemotherapy. CapeOX (oral xeloda plus oxaliplatin) is an acceptable alternative as it contains the core fluoropyrimidine + oxaliplatin backbone.

15. Indication for alternative radiation dose of fractionation regimen
16. Active Crohn's disease or another inflammatory bowel disease
17. Any T or N stage disease that is deemed unresectable by colorectal surgery without neoadjuvant therapy
18. Prior anti-PD-L1 therapy, PARPi therapy, or known germline BRCA-1/2 mutation as patients with germline BRCA-1/2 mutations have an increased risk of severe normal tissue injury to combination radiation and PARP inhibition.
19. Received a live vaccine within 14 days of initiating protocol therapy.
20. Received colony stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte macrophage colony stimulating factor, or recombinant erythropoietin) ≤ 4 weeks prior to Day 1 of protocol therapy.
21. Major surgery ≤ 3 weeks prior to Day 1 of protocol therapy (participant must recover from any surgical effects).
22. 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 Day 1 of protocol therapy.
23. Known hypersensitivity to niraparib and dostarlimab components or excipients.
24. Known grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment.
25. Known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)
26. Diagnosis, detection, or treatment of another type of cancer ≤ 2 years prior to initiating protocol therapy (except basal or squamous cell carcinoma of the skin and cervical cancer that has been definitively treated).
27. Known history of ≥ grade 3 immune-related AE with prior immunotherapy, with the exception of non-clinically significant lab abnormalities.
28. Diagnosis of immunodeficiency or has received systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to initiating protocol therapy.
29. Patients with known HIV who have documented detectable viral load or patients with a documented undetectable viral load and a CD 4 count < 350 cells within 6 months of study treatment day 1.
30. Known active hepatitis B (e.g., hepatitis B surface antigen [HbsAg] reactive) or hepatitis C (e.g., hepatitis C virus [HCV] ribonucleic acid [qualitative] is detected).
31. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
32. History of interstitial lung disease.
33. Active or uncontrolled infection necessitating hospitalization or treatment delay.
34. Known serious, uncontrolled medical disorder or nonmalignant systemic disease that preclude eligibility to undergo low anterior resection (LAR). Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, or any psychiatric disorder that prohibits obtaining informed consent
35. Pregnancy. Participant must have a negative serum pregnancy test within 72 hours prior to taking study treatment if of childbearing potential and agrees use a highly effective method of contraception from screening through 180 days after the last dose of niraparib and after the last dose of dostarlimab, or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):
    - ≥60 years of age
    - Post-hysterectomy. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound.

    See Section 5.2.1 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents.
36. Actively breastfeeding. Participant must agree to not breastfeed during the study or for 8 weeks after the last dose of study treatment.
37. Declines to use a highly effective method of contraception (see Section 5.2.1 for a list of acceptable birth control methods). Eligible patients must agree to highly effective methods of contraception starting with the first dose of study treatment through 180 days after the last dose of niraparib and dostarlimab.

5.2. LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Refrain from live virus vaccinations.
- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, [pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices] from throughout active investigational therapy (i.e., during active therapy at the start of each cycle).[35]
- Comply with their antihypertensive medications, if prescribed.
- Refrain from excessive alcohol use.
- Refrain from "natural" or "herbal" supplements unless approved by the treating physician and research team.

5.2.1. CONTRACEPTION

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

Male participants who are sexually active with partners of childbearing potential must agree to the use of a highly effective form of contraception throughout their participation beginning from the time of consent, during the study, and for 180 days after the last dose of study treatment. Male participants must not donate sperm for 90 days after receiving the last dose of niraparib.

Highly effective forms of contraception are defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence, this is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

5.2.2. BREAST FEEDING

Participants must not breast-feed while receiving protocol therapy and for 8 weeks after study treatment.

5.2.3. BLOOD AND SPERM DONATION

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

5.2.4. SCREEN FAILURES

Individuals who do not initially meet the criteria for participation in this trial (screen failure) because of a laboratory value may be rescreened as described below:

- **Pregnancy**. A woman who has recently undergone an abortive procedure may still have elevated hCG levels. In this situation, documentation from one of the treating physicians that the patient is not pregnant will suffice *in lieu* of a pregnancy test.

5.3. STRATEGIES FOR RECRUITMENT AND RETENTION

This phase 1b/2 clinical trial will employ convenience sampling with the following sampling considerations:

- Patients of all genders, races, and ethnicities are invited to participate. Under-represented race and ethnicity will be targeted for a larger phase study evaluating effectiveness.
- Consistent with ICH Good Clinical Practice E6 guidelines, this study will not include patients who cannot provide informed consent, including children, prisoners, and the mentally ill. At this time, there is no therapeutic benefit and the study's scientific rationale does not require inclusion of these patient bases. Thus, it is appropriate to delimit to only those patients who can understand the study and provide independent informed consent.
- Anticipated accrual rate is 1 every month, based upon historical trends which indicate that 3 patients meeting criteria are seen per month at UIHC.
- Up to 41 subjects will be enrolled at a single center within the United States.
- Potential participants will be identified through treating oncologists at academic medical centers from an established patient base. The treating oncologist or principal investigator will approach potential subjects, depending upon local/institutional recruitment requirements.
- Public recruitment strategies will not be employed however this study will be listed on clinicaltrials.gov
- Subjects will receive a thank-you note from the study team after completing radiation therapy and parking compensation. Research staff will maintain contact with subjects to remind about upcoming appointments and determine what would make the visit more pleasant (e.g. heated blankets, music choice, extra pillows).
- As a therapeutic oncology trial of unknown efficacy, subjects are not compensated.

6. STUDY INTERVENTION

6.1. STUDY INTERVENTION(S) ADMINISTRATION

6.1.1. STUDY INTERVENTION DESCRIPTION

6.1.1.1. NIRAPARIB® [IND 158036 (DEEMED EXEMPT) , CASTER SPONSOR-INVESTIGATOR]

Niraparib is a commercially produced biologic sold under the trade name Zejula (GlaxoSmithKline). It is FDA approved as a maintenance treatment for adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer. Use for the combinatorial treatment is granted through IND exemption 158036 (J. Caster, sponsor). Compatibility, storage & stability, as well as anticipated toxicities are outlined in the FDA approved prescribing information (package insert) as well as the manufacturer provided investigator's brochure.

6.1.1.2. DOSTARLIMAB® [IND 158036 (DEEMED EXEMPT), CASTER SPONSOR-INVESTIGATOR]

Dostarlimab (TSR-042, GSK4057190) is an investigational agent provided by GlaxoSmithKline. Investigational use for the combinatorial treatment is granted through IND exemption 158036 (J. Caster, sponsor). Compatibility, storage & stability, as well as anticipated toxicities are outlined in the manufacturer provided investigator's brochure.

6.1.2. DOSING AND ADMINISTRATION

6.1.2.1. NIRAPARIB

Initiation. Begin drug one calendar week prior to scheduled radiation therapy.

6.1.2.1.1. DOSE & ESCALATION– PHASE 1B:

Assigned per dose cohort.

Table 1: Niraparib Dose Cohorts for Phase 1b portion of study

Dose level (DL)	Niraparib Dose	Dostarlimab Dose	Radiation Dose
1 (starting)	100 mg	500 mg every 3 weeks	25 Gy (5 Gy / fraction)
2	200 mg	500 mg every 3 weeks	25 Gy (5 Gy / fraction)

Dose Modifications and Dose Delays — Phase 1b. Dose modifications and delays are not allowed for the phase 1b portion of the trial. Consult the investigator for consideration of a dose limiting toxicity.

Escalation. A traditional 3 + 3 cohort design will be used for this study. Accrual is placed on hold for the experimental arm after the last subject in each cohort receives the first dose of niraparib**. A minimum of 6 subjects must be evaluated at the recommended phase 2 dose and experience ≤ 1 DLT in total.**

Decision rules. Standard escalation rules will apply using cohorts of 3 subjects. Briefly:

- If none of the 3 subjects experiences a DLT, the dose level (DL) is escalated to 200 mg niraparib
- If 1 of the 3 subjects experiences a DLT at 100 mg, 3 more subjects are enrolled at 100 mg for further evaluation. If none of those 3 experience a DLT, the dose level is escalated to 200 mg.
- If ≥ 2 subjects experience a DLT at 100 mg, the study will be terminated.
- If ≥ 2 subjects experience a DLT at 200 mg, 100 mg is the recommended phase 2 dose for evaluation.
- If ≤ 1 subjects experiences a DLT at 200 mg, 200 mg is the recommended phase 2 dose for evaluation.

Dose limiting toxicities. Graded per CTCAE v5. A dose limiting toxicity is defined by the protocol as an unacceptable clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression or

undercurrent illness. The primary concern for pelvic radiotherapy is acute bowel toxicity. DLT assessment will continue until the start of neoadjuvant chemotherapy. The following adverse events have been defined as dose limiting toxicities for the purposes of this clinical trial:

- **Serious Adverse Event** (21 CFR 312.32) deemed related to study treatment.
- **Treatment emergent toxicity** that, in the opinion of the study investigator, requires interruption or discontinuation of radiation.
- **Treatment emergent toxicity** leading to delay of ≥6 weeks from end of experimental therapy to initiating FOLFOX chemotherapy
- **Grade 4 diarrhea**
- **Grade 3 diarrhea ≥ 14 days** despite antidiarrheal therapy
- **Grade 4 platelet count decrease ≥ 14 calendar days** as measured from AE onset.
- **Grade 3 or 4 platelet count associated with clinically significant hemorrhage.**
- **Grade 4 neutrophil count decrease ≥ 7 calendar days** as measured from AE onset.
- **≥ Grade 2 uveitis, eye pain, or blurred vision** that does not resolve with topical therapy within 2 weeks
- **≥ Grade 2 immune-related endocrine toxicity** requiring hormone replacement (except grade 2 thyroiditis or thyroid dysfunction)
- **≥ Grade 2 colitis** or diarrhea that persists for ≥ 2 weeks despite adequate steroid therapy
- **Grade 5 events** that are deemed related to study treatment.
- **A treatment emergent toxicity** that, in the opinion of the study investigator, is clinically significant and would preclude further treatment (i.e., dose limiting toxicity).

6.1.2.1.2. DOSE– PHASE 2

As defined by Phase 1b evaluation (i.e., recommended phase 2 dose)

6.1.2.1.3. ADMINISTRATION, MODIFICATIONS, AND DELAYS – ALL PHASES

Administration (all phases). Flat-fixed, continuous daily dose. 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.

Missed doses (all phases). Vomited doses should not be made up. If a participant misses a dose (greater than 12 hours from normal dosing time) of niraparib, they should skip that dose and take their next dose at its regularly scheduled time. Missed doses will not be made up.

Frequency (all phases). Once daily.

Duration. Maximum of 12 weeks of therapy.

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

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

Dose Modifications and Dose Delays — Phase 1b. Consult the principal investigator for consideration of a dose limiting toxicity.

Dose Modifications and Dose Delays – Phase 2. Treatment must be interrupted for any non-hematologic CTCAEv5 grade 3 or 4 AE the Investigator considers reasonably associated to niraparib (Table 2). If the non-hematologic toxicity is resolves to baseline or grade ≤1 within 4 weeks, treatment may resume but with a dose level reduction if

prophylaxis is not considered feasible (Table 2). If the event recurs at similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made.

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 daily, the patient must permanently discontinue treatment with niraparib.

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

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the niraparib dose, if necessary. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without niraparib dose adjustment. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Posterior Reversible Encephalopathy Syndrome (PRES): There have been rare reports (0.09% of clinical trial patients) of niraparib-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES). PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinstating niraparib therapy in patients previously experiencing PRES is not known.

Table 2: Niraparib Dose Modifications for Nonhematologic Adverse Reactions

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

The dose interruption and modification criteria for niraparib for hematologic parameters will be based on blood counts (Table 3) with stricter criteria later in treatment (after 8-10 weeks) to minimize the chances of delaying start of chemo because of ongoing cytopenias. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) treatment with niraparib must be permanently discontinued.

Table 3: Niraparib Dose Modifications for Hematologic Toxicity	
Laboratory Abnormality	Intervention
Platelet count < 100,000/μL	**Before week 10** First occurrence • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL then resume niraparib at same dose. Second occurrence • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL and then resume niraparib at a reduced dose level. • Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, if the subject has already undergone maximum dose reductions, or if original prescription is 100 mg dose. **After week 10 (any occurrence)** • Permanently discontinue niraparib and monitor blood counts weekly until platelet counts return to ≥100,000/ul
Platelet count < 75,000/ul	**Before week 8** First occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL then resume niraparib at same or reduced dose • Discontinue niraparib if the platelet count has not returned to ≥ 100,000/ul within 28 days of the dose interruption period or if the subject has already undergone maximum dose reductions. If nadir platelet count was <75,000/μL, resume at a reduced dose after recovery. Second occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. • Permanently discontinue niraparib and monitor blood counts weekly until platelet counts return to ≥100,000/ul **After week 8 (any occurrence):** • Permanently discontinue niraparib and monitor blood counts weekly until platelet counts return to ≥100,000/ul
Neutrophil count < 1,000/μL	• Withhold niraparib for a maximum of 28 days and monitor blood counts until neutrophil counts return to ≥1,500/μL and then resume niraparib at a reduced dose. • Discontinue niraparib if neutrophil level has not returned to acceptable levels within 28 days of the dose interruption period or if the subject has already undergone maximum dose reductions. **After week 10 (any occurrence):** • Permanently discontinue niraparib and monitor blood counts weekly until neutrophil counts return to ≥1500/ul
Hemoglobin ≤ 8 g/dL	• Withhold niraparib for a maximum of 28 days and monitor blood counts until hemoglobin returns to ≥ 9 g/dL and then resume niraparib at a reduced dose. • Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period or if the subject has already undergone maximum dose reductions.
Hematologic adverse reaction requiring transfusion	• For subjects 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.
Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.
Abbreviation: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; QD = once daily.	

If dose interruption and/or modification is required at any point during study treatment because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until the AE resolves to the specified blood count levels. To ensure the safety of the new dose, weekly blood draws for CBC will be required for an additional 4 weeks after the new dose is initiated.

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

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

6.1.2.2. DOSTARLIMAB

Initiation. Simultaneous with radiation therapy, after 7 calendar days of niraparib administration.

Preparation. Routine premedication prior to dostarlimab is not recommended.

Dose. 500 mg

Administration. Intravenous via a 30-minute (-5-minute/+15-minute infusion window allowed)

Frequency. Every 3 weeks.

Duration. Up to 4 doses over 12 weeks.

Dose Modifications and Dose Delays — Phase 1b. Consult the principal investigator for consideration of a dose limiting toxicity.

Dose Modifications and Dose Delays – Phase 2. Dostarlimab

Aes (both non-serious and serious) associated with dostarlimab exposure may represent an immunologic etiology. These Aes may occur shortly after the first dose or several months after the last dose of treatment.

In general, dostarlimab must be withheld for drug-related grade 3 toxicities, as well as for certain immune-related adverse events of interest (irAEIs), but may be resumed upon recovery to grade ≤1; dostarlimab will be permanently discontinued for any drug-related grade 4 AE. Dostarlimab must be permanently discontinued for certain irAEIs as described in Table 4.

The specific immune-related AEs typically observed with anti-PD-1 antibodies will be managed according to the guidelines summarized below (Table 4).[36]

6.1.2.2.1. IMMUNE-RELATED ADVERSE EVENTS OF INTEREST & GUIDELINES FOR MANAGEMENT

Given the mechanism of action of dostarlimab, it is anticipated that activation of cellular immune system can be manifested as immune-related AEs. Based on available safety data from checkpoint inhibitors, treatment emergent adverse events (TEAEs) with the specific grades listed below were selected as immune-related adverse events of interest (irAEIs). The list of irAEIs may be updated upon emerging data.

Refer to Table 4 for details on the management of dostarlimab dose delays and discontinuation for specific irAEIs. Detailed guidance for the administration of rescue medications and supportive care are available below. For all irAEIs listed in Table 4, dostarlimab should be withheld until the patient is clinically and metabolically stable and Aes have resolved to Grade ≤1. If systemic steroids are used as a part of irAEI management, the total dose of daily steroids should be equal to or less than 10mg prednisone at the time of resuming dostarlimab.

All treatment delays (including any missed doses) and discontinuations, and the reason for delays or discontinuation of dostarlimab, should be documented.

Table 4: Guidelines for Treatment of Immune-related Adverse Events of Interest		
Toxicity	AE grade	Restarting Treatment/Discontinuation
Uveitis	Symptomatic any grade	Restart when toxicity resolves to grade 0. For any recurrent uveitis or uveitis resistant to topical steroids, permanently discontinue treatment.
Diarrhea/colitis	2 to 3	Restart dosing when toxicity resolves to grade ≤1.
	4	Permanently discontinue.
AST, ALT, or increased bilirubin	2	Restart dosing when toxicity resolves to grade ≤1.
	3 or 4	Permanently discontinue (see exception below).
T1DM or hyperglycemia	3 or 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)	Restart dosing in appropriately managed, clinically and metabolically stable patients, insulin replacement therapy is required.
Immune-related encephalitis	Any grade	Permanently discontinue.
Hypophysitis	2 to 3	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to grade ≤ 1. For recurrence or worsening of grade ≥2 hypophysitis after corticosteroid taper has been completed and patient is on adequate hormone replacement therapy, permanently discontinue.
	4	Permanently discontinue.
Adrenal Insufficiency	2 to 3	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to grade ≤ 1. For recurrent or worsening ≥ 2 adrenal insufficiency while adequate hormonal replacement is continuing, permanently discontinue study drug.
	4	Permanently discontinue.
Hypo- and Hyperthyroidism	3	Hold until hormonal therapy results return to adequate levels by laboratory values and restart dosing when toxicity resolves to grade ≤ 1.
	4	Permanently discontinue.
Infusion-related reaction	2	Restart dosing when toxicity resolves to grade ≤1.
	3 or 4	Permanently discontinue.
Pneumonitis	2	Restart dosing when toxicity resolves to grade ≤1. If grade 2 recurs, permanently discontinue.
	3 or 4	Permanently discontinue.
Rash	3	Restart dosing when toxicity resolves to grade ≤1.
	4	Permanently discontinue.
Renal failure or nephritis	2	Restart dosing when toxicity resolves to grade ≤1.
	3 or 4	Permanently discontinue.
Recurrence of Aes after resolution to grade ≤1	3 or 4	Permanently discontinue.
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; T1DM = type 1 diabetes mellitus; ULN = upper limit of normal. [a] For patients with liver metastasis who begin treatment with grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week, then study treatment should be discontinued. [b] Upon resolution within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 to 50 mL/h). Otherwise, study treatment will be withheld until symptoms resolve, and the patient should be pre-medicated for the next scheduled dose.		

6.1.2.2.2. RESCUE MEDICATIONS AND SUPPORTIVE CARE GUIDELINES

During treatment with dostarlimab, patients should receive appropriate supportive care measures for Aes as deemed necessary by the treating Investigator, including but not limited to the items outlined below. Prophylactic cytokines (e.g., GCSF) should be administered according to current ASCO guidelines.

Note: It may be necessary to perform additional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the AE. Specific detailed management guidance from ASCO (2018), ESMO (2018) and NCCN (2019) for immune-mediated AE are provided in online by Association of Community Cancer Centers. Investigators should follow these recommendations for management of the following events:

- Uveitis
- Pneumonitis
- Diarrhea/colitis
- Type I diabetes and grade 3 and 4 hyperglycemia
- Hypophysitis
- Adrenal insufficiency
- Hyperthyroidism and hypothyroidism
- Hepatitis
- Renal failure or nephritis

6.1.2.2.3. MANAGEMENT OF INFUSION-RELATED REACTIONS

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 5 shows treatment guidelines for patients who experience an infusion-related reaction associated with administration of dostarlimab.

Table 5: Dostarlimab Infusion Reaction Treatment Guidelines

CTCAE grade	Treatment	Premedication at Subsequent Dosing
1	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None.
2	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Narcotics • Acetaminophen Increase monitoring of vital signs as medically indicated until subject is deemed medically stable in investigator's opinion. If symptoms resolve ≤1 hour of stopping infusion, infusion can restart at 50% of the original infusion rate. Otherwise, dosing will be withheld until symptoms resolve and subject should be pre-medicated for the next scheduled dose.	Subject may be pre-medicated 1.5 h (±30 min) prior to infusion of dostarlimab with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) • Acetaminophen 500 to 1000 mg PO (or equivalent dose of antipyretic)
	Subjects who develop grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.	

Table 5: Dostarlimab Infusion Reaction Treatment Guidelines		
CTCAE grade	**Treatment**	**Premedication at Subsequent Dosing**
3 or 4	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Epinephrine • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until subject is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated.	No subsequent dosing. **Patient is permanently discontinued from further study treatment administration.**

6.1.2.3. RADIATION THERAPY

Initiation. Simultaneous with dostarlimab, after 7 calendar days of niraparib administration.

Dose. 25 Gy. Dose specifications to targets are provided in Appendix A.

Administration. 5 Gy / fraction in IMRT or VMAT technique

Frequency. Consecutive administration, 1 fraction per day.

Duration. 5 doses over 1 week.

Delays or Modifications. None. Consider dose limiting toxicity if a break is indicated.

6.2. PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1. ACQUISITION AND ACCOUNTABILITY

6.2.1.1. NIRAPARIB

Niraparib is an orally available, potent, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) -1 and -2 inhibitor. Niraparib is also known commercially as ZEJULA. Niraparib will be provided by GlaxoSmithKline (GSK) under the investigator-sponsored IND. Niraparib will be shipped to, and maintained, by the designated research pharmacy on site.

6.2.1.2. DOSTARLIMAB

Dostarlimab (TSR-042) Dostarlimab is a humanized mAb that binds to PD-1 and blocks the interaction between PD-1 and ligands PD-L1 and PD-L2. Dostarlimab is produced by recombinant DNA technology in a mammalian expression system using a stable Chinese hamster ovary (CHO) cell line. This investigational IgG4 antibody is supplied by GlaxoSmithKline under the investigator-sponsored IND. Dostarlimab will be shipped to, and maintained, by the designated research pharmacy on site.

6.2.2. FORMULATION, APPEARANCE, PACKAGING, AND LABELING

6.2.2.1. NIRAPARIB

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

6.2.2.2. DOSTARLIMAB

There is currently one dostarlimab drug product presentation being used, 50 mg/mL dostarlimab with a delivery volume of 10.0 mL and with the following formulation: dostarlimab, citrate, arginine, sodium chloride, and polysorbate 80. The drug product is a sterile solution in citrate buffer (pH 6.0±0.5) supplied as single-use vials for IV administration. Dostarlimab is provided as a liquid formulation in a citrate buffer (pH 6.0±0.5). The drug product is a sterile, clear-to-slightly opalescent, colorless-to-yellow solution, essentially free from visible particles The dostarlimab 50-mg/mL drug product presentation is aseptically processed; sterility is confirmed through sterility testing of the drug product. Dostarlimab is provided for injection is supplied in vials containing 500 mg at a concentration of 50 mg/mL.

6.2.3. PRODUCT STORAGE AND STABILITY

6.2.3.1. NIRAPARIB

All study treatment supplies must be stored in accordance with the manufacturer's instructions and package labelling. Until dispensed to the participants, the study treatment will be stored in a securely locked area, accessible to authorized personnel only. Niraparib should be destroyed at the investigational site if permitted by local regulations.

6.2.3.2. DOSTARLIMAB

Dostarlimab is aseptically filled into 10 mL (50 mg/mL) Type 1 borosilicate clear glass vials, stoppered with a chlorobutyl elastomer stopper laminated with fluoropolymer and sealed with an aluminum overseal with a flip-off cap. Expiration date is printed on the product label. The product should be stored between 2°C and 8°C, Dostarlimab should be destroyed at the investigational site if permitted by local regulations.

6.2.4. PREPARATION

6.2.4.1. NIRAPARIB

Not applicable; oral agent.

6.2.4.2. DOSTARLIMAB

Preparation instructions for dostarlimab can be found in the TSR-042 IST Product Storage and Handling Manual.

6.3. MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1. PHASE 1

The phase 1 portion of the clinical trial utilizes dose limiting toxicity as the primary endpoint. As such, bias is minimized by using independent monitors to review subject medical records and study casebooks to evaluate if adverse events were assessed appropriately and dose limiting toxicities identified as per protocol. Prior to dose escalation or expansion to phase 2, an independent data and safety monitoring committee (Holden Comprehensive Cancer Center, University of Iowa) will review all data to determine the appropriateness of the request.

6.3.2. PHASE 2 EXPANSION

As an early phase 2 study to determine initial efficacy and effect size, this clinical trial is designed as an open-labelled, non-randomized, single arm study to provide initial data to support a well-controlled effectiveness study.

To minimize bias, a single blind will be used for any radiologic evaluations for this study. A centralized reviewer will evaluate CT scans per RECIST 1.1. The reviewer will not be informed if they are reviewing interventional images. *In lieu* of a concurrent control, serialized CT scans from University of Iowa's imaging repository or from the comparator cohort will be used. Dates will be stripped from the CT images. Images will include only:

- Subject ID
- Series of imaging

An independent, in-house CRA will assign an imaging sequence number unique to the subject and the study visit. This code will provide a link for RECIST results while maintaining a blind during imaging and dosimetry evaluation.

Subjects, the investigator and research team, and the treating oncologists will not be blinded to the subject's therapy.

6.4. STUDY INTERVENTION COMPLIANCE

All interventions in this protocol are administered by licensed medical staff. For this reason, adherence to protocol will be assessed through source document verification in the electronic health records for:

- Pill diary and drug reconciliation for niraparib
- Prescription, dispense, and administration of dostarlimab infusions

6.5. CONCOMITANT THERAPY

For the purposes of this protocol, a concomitant therapy is considered to be any of the following:

- Prescription medication from an authorized prescriber
- Over the counter medications
- Complementary or alternative medications, including herbal remedies or supplements

6.5.1. MEDICATION LOG

A concomitant medication log, separate from the participant's medical chart, will not be maintained for the purposes of this trial. However, appropriate medical staff will review concomitant medications prior to each cycle with the subject so the medications can be reviewed if an untoward event occurs during the study. **Changes to blood pressure medication should be noted and sent forward to the study investigator**.

6.5.2. POTENTIAL INTERACTIONS

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. For further information, consult the Investigator's Brochure.

6.5.3. INVESTIGATIONAL DRUGS AND/OR DEVICES

Subjects may not receive any investigational drug and/or device during the course of the study except for experimental imaging agents. Standard-of-care / routine off-label use is acceptable and not considered investigational.

6.5.4. PROHIBITED MEDICATIONS

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 and/or dostarlimab.
- Systemic glucocorticoids for any purpose other than to manage symptoms of suspected irAEIs. (Note: Use of inhaled steroids, local injection of steroids, topical steroids, and steroid eye drops are allowed). If medically deemed necessary (e.g., acute asthma or chronic obstructive pulmonary disease exacerbation, etc.), Investigators are allowed to use their judgment to treat patients with systemic steroids. In all cases, systemic steroids should be tapered to ≤ 10mg of prednisone or equivalent prior to the next dose of dostarlimab.
- Live vaccines within 14 days prior to the first dose of study treatment Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, 33acilli Calmette Guerin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.
- COVID (SARS-CoV-2) vaccinations. Please follow the current FDA guidance regarding vaccination.

  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.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. DISCONTINUATION OF STUDY INTERVENTION

Participants who withdraw after consenting to the clinical trial, but do not receive a dose of niraparib will not be followed for this clinical trial.

Participants who withdraw after receiving at least 1 dose of niraparib but do not receive radiation will be followed as an intent-to-treat population. If the participant withdraws full permission (i.e., revokes HIPAA authorization), the participant will not be followed further, but all data obtained until the date of HIPAA revocation will be used for the purposes of this study. Subject's intent must be well documented in the case book.

A subject's discontinuation of the study intervention (i.e., declining further study treatment) does not define the subject as being off-study (protocol section 7.2). **If the subject consents to it, all study procedures should continue**

even in the absence of study treatment. Subjects who decline further treatment should be reviewed for a dose-limiting toxicity by the investigator and DSMC.

- **Dose limiting toxicity.** During the phase 1b portion of the trial, If the subject experiences a dose limiting toxicity, the subject will be withdrawn from treatment and followed as per protocol. The investigator must notify the DSMC within 1 business day and file with the IRB of record.
- **Subject declines further study intervention.** If a subject who has received at least one dose of niraparib declines further study intervention, the reason for declining treatment should be documented – specifically, if it is due to an adverse event.
- **Unforeseen medical event.** If a subject undergoes a medical event that compromises the subject's safety or study's endpoints, the subject may be withdrawn from treatment. The sponsor or investigator may make this determination. If a subject is withdrawn for this reason, the subject must be followed for a minimum of 30 calendar days from the last injection with investigational product.
- **Pregnancy**. If a subject declares pregnancy, the subject will be withdrawn from treatment. The DSMC will be notified within 1 business day of the event and an unanticipated problem will be filed with the IRB of record. Subject should be asked to consent to have the pregnancy followed (as appropriate).
- **Subject non-compliance.** If a subject does not comply with the required adverse event assessment (i.e., hematologic and serum chemistry assessments, follow-up assessments), study treatment may be discontinued to reduce risk to the subject.

7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subject participation may be discontinued (i.e. withdrawn from study without further follow-up or interaction) in the following circumstances:

- **Subjects who decline to receive any study treatment after consenting** to the clinical trial are withdrawn from study and are not followed for this clinical trial.
- **Investigator non-compliance**. If an investigator is considered to be non-compliant with the study protocol or federal, state, local, or institutional requirements, the sponsor may end the study and withdraw subjects from trial.
- **Subject refusal to continue.** Subjects who decline further study follow-up (i.e. no longer wish to undergo study assessments) are withdrawn from the study. If the participant withdraws full permission (i.e., revokes HIPAA authorization), the participant will not be followed further, but all data obtained until the date of HIPAA revocation will be used for the purposes of this study. Subject's intent must be well documented in the case book.
- **Termination of study.** If the study is terminated for any reason, the subject will be followed for a minimum of 30 calendar days for safety assessment, including hematologic and serum chemistries as prescribed per protocol.

The reason for participant discontinuation or withdrawal from the study will be recorded in the subject's casebook and entered into the electronic data capture system (EDC).

Phase 1 subjects who withdraw after initiating combined therapy will be reviewed by the principal investigator to determine the appropriateness of replacement vs. reporting a dose limiting toxicity.

Phase 2 subjects who undergo 1 cycle of combined therapy and subsequently withdraw (or are withdrawn) may be replaced at the discretion of the sponsor and the statistician.

7.3. LOST TO FOLLOW-UP

A subject is considered lost to follow-up for the purposes of this trial if one of the following criteria are met:

- Cancels (without explanation) or fails to appear for treatment
- Does not return follow-up phone calls from research staff (three attempts, minimum)
- Written notice (certified mail) to subject returns 'address unknown.'

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- **Safety assessments.** The site will attempt to contact the participant and reschedule missed laboratory assessments or physical exams within 3 business days. Research staff or the treating study physician should counsel the participant on the importance of safety assessments. **Site research staff will ask the subject if they are willing to continue in the study**. If subject has seen local practitioner *in lieu* of UIHC oncologist, obtain release of information and obtain local provider notes. **A participant's failure to return to the study site for assessments is not considered a deviation if local assessments can be obtained as per study calendar.**
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up. This should be reported to the IRB of record per institutional policies.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. EFFICACY ASSESSMENTS

8.1.1. BASELINE ASSESSMENTS

The following should be completed within 21 days of therapy day 1. Assessments already completed for standard of care can be utilized in compliance with institutional procedures and HIPAA compliance. All assessments are completed using CTCAE v5.

Although adverse events are being examined for an efficacy endpoint to determine the combined therapy's effect on symptoms of treatment and/or disease, they are foundation of safety assessment for investigational agents. **For this reason, adverse event collection is described under section 8.2**.

1. **Diagnostic CT scan**. Verify a chest/abdomen/pelvic CT scan was done within 3 months of initiation of experimental therapy. If not, order a new diagnostic CT to provide baseline RECIST criteria. An MRI is an acceptable alternative if approved by the PI.
2. **Pelvic MRI**. The pelvic MRI will be obtained for tumor staging purposes (pre-therapy) and used to assist in disease response evaluation. EUS can be used for pre-therapy tumor staging for patients unable or unwilling to undergo contrast-enhanced pelvic MRI.
3. **Peripheral CD4 / CD8 lymphocytes.**
4. **Mutation analysis**. Pathologic tissue specimens will be assessed for tumoral MSS/MSI, KRAS, and BRAF mutational status in addition to PD-L1 IHC. Exempted from 21 day window.
5. **Tumor infiltrating lymphocytes** will be assessed using existing pathologic tissue specimens. Exempted from 21 day window.

8.1.2. ACTIVE THERAPY

The following data will be collected during active therapy to determine initial efficacy:

6. **Peripheral CD4/CD8 lymphocytes**. Obtain once at midpoint during study (study weeks 7 through 9), once at end of study drug administration (week 12), and one draw anytime during cycle 4 of the subsequent neoadjuvant chemotherapy.
7. **Tumor Infiltrating Lymphocytes**. Evaluate from biopsy obtained during sigmoidoscopy during week 8 of study therapy (± 1 week) and in final tumor pathology specimen if residual viable tumor is present in patients undergoing surgery.
8. **Flexible sigmoidoscopy / anoscopy with tumor biopsy**. Schedule for 6 weeks post-RT (study week 8)
9. **Patient Reported Outcome Measures (PROMs)**. Administer on study day 1, study day 8, on the day of each infusion, and during the physical exams during the DLT toxicity window. Note level of assistance given, if any.
10. **Pelvic MRI.** A standard of care contrast-enhanced MRI will be obtained approximately 6 weeks post-RT (study week 8) to assess tumor response to therapy.

8.1.3. ACTIVE FOLLOW-UP

With the exception of the surgical assessment for clinical response, protocol prescribed **active follow-up is until the start of FOLFOX chemotherapy** to define dose limiting toxicities (phase 1b) and 24 months from the end of radiation therapy to define tumor response (both phases). The following data will be collected during the follow-up phase of the study:

- **Surgical assessment**. Completed as per standard of care. Reports used to determine need for surgery, as well as any imaging, should be obtained to support primary objective.
- **Standard of care imaging.** Any CT or MR imaging obtained for routine clinical follow-up will be used to assess efficacy of treatment. Appropriate authorization should be obtained if from an outside institution. Digital images should be obtained and archived for the study.
- **PROM.** Have subject complete their PROM at 1, 6, 12, and 24 months post-radiation. Note level of assistance given (if any). This can be administered in person, over the phone, or by mail. Method of administration should be noted in the case-binder.

8.1.4. LONG TERM FOLLOW-UP

After completing active follow-up, data will be collected twice per year to assess progression (as appropriate) and overall survival status. Given appropriate institutional approval and authorizations, this can be done through chart review, phone call to the participant, or contacting a local provider. Subject will be followed until the study is completed, the subject succumbs to disease, or the subject withdraws consent for further study follow-up.

8.2. SAFETY AND OTHER ASSESSMENTS

8.2.1. HISTORICAL INFORMATION

The following data should be mined, if available, from the subject's existing medical records. If information is available from outside medical facilities, the investigator and research staff are requested to obtain appropriate authorization from the subject to obtain copies of these data. **Only the most recent imaging should be obtained for each category** (e.g., MRI, CT, PET/CT).

- **MRI**, performed ≤ 1 year from date of consent
- **CT scan,** performed ≤ 1 year from date of consent

- **Significant medical conditions**, defined as those conditions that could contribute to underlying health conditions or treatment-emergent adverse events. Examples include, but are not limited to, hypertension, prior myocardial infarction, seizures, and sepsis.
- **Metabolic and hematologic baselines**. Baseline metabolic and hematologic conditions will be obtained from screening labs and/or any hematology or comprehensive metabolic panels. These conditions will be marked as "active," in the electronic database (EDC) and graded per CTCAE v.5. If subjects have a long standing and established hematologic (e.g., anemia) or metabolic (e.g., hyperglycemia) condition that is not captured on screening or baseline lab assessments, this will be marked as "past," or "not current," in the EDC and severity of the prior event can be provided in a comment in the EDC.

8.2.2. BASELINE ASSESSMENTS [ALL SUBJECTS]

The following should be completed within 21 days of therapy day 1. Assessments already completed for standard of care can be utilized in compliance with institutional procedures and HIPAA compliance. All assessments are completed using CTCAE v5. All lab tests should be reviewed and documented through routine clinical practices (i.e., EHR).

- **Physical exam.** Complete physical exam including a medical history review.
- **Vitals**. Temperature, heart rate, blood pressure, weight. Blood pressure must be obtained in seated position. Document in electronic health record.
- **CBC w/differential**.
- **Comprehensive Metabolic Panel**. Must include glucose, serum creatinine, total bilirubin, aspartate aminotransferase and alanine aminotransferase at minimum.
- **Thyroid panel**. Testing should include TSH, T3 or FT3, and FT4.
- **Solicited adverse events.** Quantify nausea, vomiting, baseline bowel habits, fatigue, and pain (note location of pain, if any). Note etiology, if available. The staff interviewer may review participants provided PROM but cannot query the participant directly about their answer; it should be used as a guide only.
- **Unsolicited adverse events.** Ask participant if there are any other symptoms they are experiencing through general query. If participant endorses a symptom, note etiology, if available.
- **Concomitant medications.** Reconcile concomitant medication with indication, frequency, and active use in the medical record.

8.2.3. ACTIVE THERAPY

The following data will be collected to assess safety and further determine the adverse event profile of this combination therapy.

1. **Blood pressure**. Obtain blood pressure pre- and post-infusion with each infusion. Pre-infusion is same day, any time prior to the beginning of infusion. Post infusion is defined as ≤ 15 minutes after end of infusion. Blood pressure and heart rate must be monitored weekly through study W8, then monthly through end of DLT window (phase 1b) or until chemotherapy begins (phase 2). Patients may monitor blood pressure and heart rate at or near home.
2. **Physical exam.** Perform at the last radiation treatment (and then within 1 business day prior to each dostarlimab infusion. Physical exams are also performed for dose limiting toxicity assessment, study week 16 (ideally day 113) and study week 21 (ideally day 152). At minimum, physical exam will be symptom directed and include performance status, weight, blood pressure, and heart rate. Physical exams may be performed by appropriately licensed and credentialled personnel (MD, PA-C, or ARNP).
3. **Pregnancy test.** For individuals of childbearing potential, a pregnancy test must be resulted within 72 hours prior to the first dose of niraparib and within 72 hours before each dostarlimab infusion.
4. **CBC w/diff**. A complete blood cell count with differential should be drawn weekly. Lab review should be documented through routine clinical practices (i.e., EHR).
5. **Comprehensive Metabolic Panel**. Must include glucose, serum creatinine, total bilirubin, aspartate aminotransferase and alanine aminotransferase at minimum. Draw once during radiation therapy, and

then within 72 hours prior to each dostarlimab infusion. Lab review should be documented through routine clinical practices (i.e., EHR).

6. **Thyroid panel**. Testing should include TSH, T3 or FT3, and FT4. Thyroid panel should be ordered after 4 weeks of niraparib therapy and then ordered at least every 6 weeks.
7. **Solicited adverse events.** Quantify radiation dermatitis, diarrhea, nausea, mucositis, fatigue, and rash. Note etiology, if available. The staff interviewer may review participant's provided PROM but cannot query the participant directly about their answer; it should be used as a guide only. AEs should be assessed study day 1, day 1 of radiation therapy, on last day of RT, and then at minimum at each infusion. Phone assessments are acceptable.
8. **Unsolicited adverse events.** Ask participant if there are any other symptoms they are experiencing through general query. If participant endorses a symptom, note etiology, if available. This should be assessed study day 1, day 1 of radiation therapy, on last day of RT, and then at minimum at each infusion
9. **ECG.** Order ECG with clinical interpretation during study week 14 and study week 21 and document in electronic health record.
10. **Concomitant medications.** Reconcile concomitant medication with indication, frequency, and active use in the medical record on RT day 1 and then at each dostarlimab infusion.

8.2.4. ACTIVE FOLLOW-UP

Protocol prescribed **until the start of FOLFOX neoadjuvant chemotherapy** to define dose limiting toxicities (phase 1b) and 24 months from the end of radiation therapy to define tumor response (both phases). The following data will be collected during the follow-up phase of the study:

- **CBC with differential**. Order at end of treatment appointment at week 16. Must be drawn prior to any secondary chemotherapy.
- **Serum chemistries.** Order at end of treatment appointment at week 16. Must be drawn prior to any secondary chemotherapy.
- **Thyroid panel**. Order at end of treatment appointment at week 16. Must be drawn prior to any secondary chemotherapy.
- **Changes to antihypertensive therapy**. Changes to blood pressure medications should be noted and sent forward to the study principal investigator.
- **Exam notes**. If subject no longer returns to UIHC for routine oncologic care, copies of physical exams and physician notes for routine follow-up should be obtained. Enter into local EHR as per standard institutional practice. Appropriate authorization should be obtained for access to information.
- **Emergency room / admission documents**. If subject is seen at an emergency room or admitted for any reason within 24 months of completing radiation therapy, at minimum discharge summary should be obtained. The preferred information is intake summary, initial history and physical, and discharge summary. Supporting laboratory, radiology, and surgery notes are also required.

8.2.5. LONG-TERM FOLLOW-UP

Safety data are not collected beyond 2-years post-therapy unless there is an untoward event that cannot be otherwise explained (disease, medical history, chemotherapy, other treatments).

8.3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1. DEFINITION OF ADVERSE EVENTS (AE)

This study follows the United States Food & Drug Administration's definition of adverse event (AE). Specifically, the term 'adverse event' means any untoward medical occurrence associated with the use of an intervention in humans, **whether or not considered intervention-related** (21 CFR§312.32(a)). 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.

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

8.3.2. DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- a congenital anomaly/birth defect.

An important medical event is one that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgement, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, or transmission of disease associated with the administration of the study drug.

8.3.3. ADVERSE EVENT OF SPECIAL INTEREST (AESI) FOR NIRAPARIB

An Adverse Event of Special Interest is defined as any Serious AE that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication of serious events to GSK is required.

Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML), as well as other secondary cancers, should be reported to GSK upon awareness for any subject who has received niraparib (regardless of the timeframe since the last dose).

8.3.4. CLASSIFICATIONS OF AN ADVERSE EVENT

Severity

All adverse events, regardless of attribution, will be graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 5. Investigators will be provided sponsor-developed quick-start guides and instructions for adverse events of special significance.

Relationship to Study Intervention

Due to the small sample size and oncologic nature of this study leading to an anticipated toxicity profile, adverse events that are mild or moderate (i.e., CTCAE grade 1 or 2) will not be evaluated for attribution to the investigational medical product.[37]

Attribution to the investigational medical therapy is required for:

- grade 3 or 4 events
- Serious adverse events

Initial assessment may be made by any research team member with appropriate delegation. Final assessment must be determined by the site's investigator. Temporal relationship must be considered as well as pharmaceutic properties. The following definitions are provided as guidance:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

For purposes of FDA reporting, the Sponsor-Investigator is responsible for final determination of relationship to study intervention.

Expectedness

Expected adverse reactions (i.e., adverse events associated with the use of the drug) are AEs that are known to occur for the study intervention being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Identify the source of the reference safety information used to determine the expectedness of the AE (e.g., IB, approved labeling). Expectedness is assessed based on the awareness of AEs previously observed, not on the basis of what might be anticipated from the properties of the study intervention.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB, package insert, or approved labeling or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the protocol, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB or package insert referred

only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB or package insert listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB, package insert, or labeling as occurring with a class of drugs (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the study intervention, but are not specifically mentioned as occurring with the particular study intervention under investigation.

The Sponsor-Investigator of the IND will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Anticipated
Anticipated adverse events are AEs that are known to occur for the study population, condition under study, or standard treatment for the condition under study.[37] These events are established through peer-reviewed literature, U.S. prescribing information for standard therapies, and conventional medical texts. Anticipated events well established for the condition, its therapy, or the patient population should be described in the investigational plan and the expected frequency of the events provided with appropriate citations.

Shifts in frequency, severity, or onset of anticipated events must be considered as an adverse reaction related to the investigational medical product. Such changes in anticipated events should be identified through established statistical methods as available. The sponsor is responsible for identifying these shifts through data and safety review. Once a shift has been identified it should be reported to FDA as per 21 CFR 312.32 with investigators appropriate informed.

8.3.5. TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be documented in the participant's casebook and then entered into the appropriate case report form (CRF). Information to be collected includes event description (i.e., CTCAE v5 term), date of onset, clinician's assessment of severity (i.e., CTCAE grade), association to the investigational product(s), and date of resolution (or new baseline, resolved with sequelae). All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Similarly, if the etiology appears to change (i.e., a rash that disappears and then returns), this may be captured as an adverse event at the discretion of the research team / study investigator.

This study will utilize toxicity over time reporting. This requires changes in AE severity to be documented with appropriate start and stop dates, enabling an assessment of how many days of the adverse event the subject experienced. **The use of the term 'intermittent' is not allowed** by the sponsor as a modifier. Any adverse event described by the subject should have start & stop dates listed as completely as possible capturing onset and duration of each episode.

As per Federal Code and ICH E6, the principal investigator has overall authority for the recording, assessment, and attribution of each adverse event. The principal investigator may delegate identification, recording, and initial assessment to those individuals believed to have appropriate training and experience. The principal investigator must provide final approval on all adverse event data. All adverse events will be followed through 90 days or resolution. All serious adverse events will be followed until resolution (i.e., return to baseline or establishment of a new baseline for that subject).

- **Solicited AEs**. Adverse events for radiation dermatitis, diarrhea, nausea, mucositis, fatigue, and rash will be queried by staff as described in section 8.2. Adverse events will also be collected directly from the participant using the NCI's PRO-CTCAE system.
- **Unsolicited AEs.** Other adverse events not directly queried will be mined from clinical notes during the time frames specified in protocol section 8.2. Additionally, these adverse events will be collected using the question, "Have you noticed anything new or different since you received the injection of the investigational drug?"

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 AEs and SAEs will be collected from administration of the first treatment and must be throughout the study and for at least 90 days after the last dose of protocol therapy.

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

8.3.6. ADVERSE EVENT REPORTING

Routine adverse events will be reported to the sponsor and the Data and Safety Monitoring Committee (DSMC) through routine electronic data capture utilizing the OnCore clinical trials management system.

8.3.6.1. DETERMINATION OF RELATIONSHIP TO INVESTIGATIONAL PRODUCT

The clinical research team is responsible for collecting and recording the research data. As these results are collected, all toxicities and adverse events will be identified and reported to the principal investigator (PI). The principal investigator (PI) will determine final relationship of the event to the investigational medical therapy (Niraparib, Dostarlimab, and the combinatorial therapy):

- grade 1 and 2 events do not require attributions assigned.
- grade 3 and higher adverse events require attribution assigned to niraparib, dostarlimab, radiation therapy, and the combined regimen.
- All serious adverse events (SAEs) require attribution to niraparib, dostarlimab, radiation therapy, and the combined regimen.

Toxicity will be graded according to NCI's Common Toxicity Criteria (CTCAE v5). The principal investigator will have final responsibility for determining the attribution of toxicity as it is related to the investigational product when reported to the sponsor. The sponsor will have final responsibility for assessing relationship to the investigational product when considering reporting requirements under 21 CFR 312.32

8.3.7. SERIOUS ADVERSE EVENT REPORTING

Any serious adverse events to niraparib, dostarlimab, and/or the combined regimen will require a notification to the DSMC within 1 business day followed by complete report within 5 calendar days. These expedited adverse event reports (requirements listed below) will be reviewed by the DSMC. The investigator will continue to follow or obtain documentation until the resolution of such an event until it is resolved (with or without sequelae).

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

8.3.7.1. SPONSOR NOTIFICATION

The Sub-Investigator or designee, will report to the Sponsor-Investigator **within 1 business day** any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention

caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must follow SAE reporting requirements.

The Sponsor-Investigator will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.]

8.3.7.2. GSK NOTIFICATION

8.3.7.2.1. SAES (INCLUDING BY DEFAULT SERIOUS AESI)

The Sponsor Investigator must report all SAEs and all follow up information to GSK on a GSK-specific SAE Report Form with accompanying coversheet within **1 business day** of becoming aware of the initial event or clinically significant follow-up information.

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

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

8.3.7.2.2. PREGNANCIES

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 GSK product including follow up outcomes to GSK within 24 hours of awareness.

Each pregnancy must be reported on an Initial Pregnancy Report Form within one business day 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 GSK within 1 business day. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

GSK SAE, Pregnancy, and Serious AESI Reporting Information
Email: OAX37649@gsk.com Fax: +44(0) 2081814780

8.3.7.2.3. REPORTING PRODUCT COMPLAINTS FOR GSK PRODUCTS

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

8.3.8. REPORTING EVENTS TO PARTICIPANTS

The Sponsor-Investigator will review all reported serious adverse events and determine the appropriateness of changes to the informed consent document. The sponsor-investigator will notify investigators if re-consenting subjects is mandatory for all subjects or only for those currently undergoing investigational procedures. If the sponsor-investigator does not believe re-consenting is mandatory, the investigator may require re-consent for those all subjects or just those subjects undergoing investigational procedures.

The institutional review board of record will be made aware of serious adverse events consistent with institutional policy. The sponsor and investigator will defer to these IRBs if requested to change the risk section of the informed consent document. Similarly, the sponsor will also defer to the IRBs if it is determined re-consent should be mandatory.

8.3.9. REPORTING OF PREGNANCY

If a study participant is discovered to be pregnant after administration of the investigational products, the sponsor will be notified within 1 business day. The Sponsor-Investigator will provide dosimetric estimates to share with the participant's physician(s). The institutional review board of record will be notified. The participant and fetus will be followed through delivery. If a separate consent is required from the IRB of record, this consent will be requested from the participant.

8.4. UNANTICIPATED PROBLEMS

8.4.1. DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem.

Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs. Examples of unanticipated problems provided by OHRP:

- Clinical trial data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work.
- As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation.
- Subjects with cancer are enrolled in a phase 2 clinical trial evaluating an investigational biologic product derived from human sera. After several subjects are enrolled and receive the investigational product, a study audit reveals that the investigational product administered to subjects was obtained from donors who were not appropriately screened and tested for several potential viral contaminants, including the human immunodeficiency virus and the hepatitis B virus.

8.4.2. UNANTICIPATED PROBLEM REPORTING

Adverse event as an unanticipated problem
An adverse event, or serious adverse event, also meeting the definition of an unanticipated problem will follow the adverse event reporting pathway for sponsor-investigators.

Investigator-identified non-adverse event unanticipated problems
Institutional Review Board. The sponsor-investigator will report unanticipated problems (UPs) to the Institutional Review Board (IRB) of record as per their policy.

Sponsor-investigator. The investigator will provide information to the sponsor-investigator within 1 business day. The report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

Additional requirements. Other reporting (institutional, local, or state) may be required by the investigator.

Sponsor-investigator -identified non-adverse event unanticipated problems
A sub-investigator and/or research team member will notify the sponsor-investigator no less than 1 calendar week after being notified of the unanticipated problem. The sponsor-investigator will then notify the IRB of record as per their policy as well as follow any other reporting (institutional, local, or state) that may be required.

8.4.3. REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The sponsor-investigator will review all unanticipated problems and determine the appropriateness of changes to the informed consent document. The sponsor-investigator will notify sub-investigators if re-consenting subjects is mandatory for all subjects or only for those currently undergoing investigational procedures.

The sponsor-investigator will defer to these IRBs if requested to change the risk section of the informed consent document. Similarly, the sponsor-investigator will also defer to the IRBs if it is determined re-consent should be mandatory.

9. STATISTICAL CONSIDERATIONS

9.1. STATISTICAL HYPOTHESES

Phase I: The primary objectives of Phase 1 are to assess safety and tolerability and determine the maximum tolerated dose (MTD) of niraparib in combination with dostarlimab and hypofractionated radiotherapy. The MTD will be established using a traditional 3+3 design and will be defined as the highest dose level in which ≤1 out of 6 patients experience a dose limiting toxicity (DLT). There are no formal and testable hypotheses for efficacy endpoints in Phase 1.

Phase 2: The primary objective of Phase 2 is to determine whether treatment with the combination niraparib, dostarlimab and hypofractionated radiotherapy, as part of TNT will increase the clinical complete response (cCR) rate in locally-advanced rectal cancer patients. Randomized trials utilizing TNT have reported cCR rates ranging from 30 to 45%. In the RAPIDO trial, patients randomized to TNT with upfront short course radiation had a cCR rate of 42%. The investigational regimen is anticipated to increase the cCR rate to 65%. In statistical terms, we are testing the null hypothesis H_o: cCR rate ≤ 42% versus the alternative H_1: cCRrate > 65%.

9.2. SAMPLE SIZE DETERMINATION

Phase 1: Sample size requirements are dependent on the occurrence of DLTs. Up to 12 patients will be treated in this phase.

Phase 2: When testing the null hypothesis that the cCR rate is less than or equal to 42% versus the alternative that the cCR rate is greater than 65%, a sample size of 32 patients ensures 80% power to detect an absolute increase of 23% (from 42% to 65%) using a one-sided binomial exact test with a 5% significance level. If 19 or more of the 32 patients have a cCR, the treatment may be deemed worthy of further investigation.

The 6 patients treated at the MTD in Phase 1 will be included in the Phase 2 efficacy evaluation, which requires a total of 32 patients. A total of up to 38 patients will be enrolled in this study.

Based upon historical trends which indicate approximately 3 patients meeting inclusion criteria are seen monthly at UIHC (36/year), the anticipated accrual rate is 1 patient per month (12/year).

9.3. POPULATIONS FOR ANALYSES

The safety population includes all patients who received at least one dose of combined therapy (niraparib, dostarlimab, radiation therapy). The safety population will be the analysis population for the safety analyses.

The intent-to-treat (ITT) population is defined as all patients meeting inclusion criteria who received at least one dose of combined therapy (niraparib, dostarlimab, radiation therapy), irrespective of their compliance to the planned course of treatment. The ITT population will be the analysis population for the efficacy analysis.

9.4. STATISTICAL ANALYSES

9.4.1. GENERAL APPROACH

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by count and proportion.

9.4.2. ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy endpoint is cCR rate. Clinical complete response (cCR) will be defined as the absence of definitive residual tumor cells in the primary site or regional nodes on post-treatment pelvic MRI and endoscopic examination. Post-treatment changes, such as scarring, are common and often it can be difficult to distinguish benign post-treatment changes from residual tumor on post-treatment MRIs. In cases where equivocal changes are noted in the tumor bed on MRI but the primary colorectal surgeon determines there is no evidence of residual disease on endoscopy, the subject will be considered a cCR. A one-sided p-value for a test of the null hypothesis that the cCRrate is less than or equal to 42% versus the alternative that it is greater than 65% will be computed based on a binomial exact test using the ITT population. In addition, a binomial proportion and one-sided 95% exact confidence interval will be reported.

9.4.3. ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary efficacy endpoints will be summarized descriptively using the ITT population.

- **Pathologic Complete Response (pCR) Rate** is defined as the proportion of patients with a pCR defined as the absence of viable tumor in the primary tumor bed and all regional nodes among patients with LARC involving the high rectum recommended to undergo surgical resection. A binomial proportion with a 95% exact confidence interval will be reported.
- **Organ Preservation** is defined as time from treatment initiation (day 1) to date of rectal resection (TME or APR) for persistent disease after neoadjuvant therapy, local recurrence after an initial cCR, or compromised bowel function (regardless of attribution to study drugs, radiation, or chemotherapy). Analysis of this endpoint will be restricted to patients with tumors in the low and mid rectum as patients with tumors in the high rectum will undergo resection regardless of their response to therapy. Patients who have less than a cCR and refuse surgery will be censored on the date surgery was formally recommended by the treating colorectal surgeon. Otherwise, the patient will be censored at their last follow up. Cumulative organ preservation will be summarized over time with the method of Kaplan-Meier.
- **Overall Survival** (OS) is defined as the time from treatment initiation (day 1) to the date of death due to any cause. Patients who do not die during the study period will be censored at their last date known to be alive. Cumulative OS will be descriptively summarized over time with the method of Kaplan-Meier.
- **Progression Free Survival** (PFS) is defined as the time from treatment initiation (day 1) to the date of first documentation of disease progression (per RECIST 1.1) or death due to any cause in the absence of documented progression. Otherwise, the patient will be censored at their last assessment for progression. Cumulative PFS will be descriptively summarized over time with the method of Kaplan-Meier.
- **Metastasis Free Survival** (MFS) is defined as the time from treatment initiation (day 1) to the date of first documentation of disease progression outside of the pelvis (per RECIST 1.1) or death due to any cause in the absence of documented progression. Otherwise, the patient will be censored at their last assessment for progression. Cumulative MFS will be summarized over time with the method of Kaplan-Meier.
- **Local Recurrence Free Survival** (LRFS) is defined as the time from treatment initiation (day 1) to the date of first documentation of disease progression within the pelvis (per RECIST 1.1) or death due to any cause. Otherwise, the patient will be censored at their last assessment for progression. Cumulative LRFS will be summarized over time with the method of Kaplan-Meier.

- **Ostomy-Free Survival** (OFS) is defined as the time from treatment initiation (day 1) to receipt of permanent ostomy (includes colostomy or end ileostomy) or death due to any cause. Otherwise, the patient will be censored at their last date of follow-up. Cumulative OFS will be summarized over time with the method of Kaplan-Meier.
- **Objective Response Rate** (ORR) is defined as the proportion of patients with a response of CR or PR (per RECIST 1.1) at 3 months post-radiation. A binomial proportion with a 95% exact confidence interval will be reported.
-

9.4.4. SAFETY ANALYSES

The incidence of treatment-emergent adverse events will be summarized by system organ class and/or preferred term, type of adverse event, severity (based on NCI CTCAE v5 grades), and relation to study treatment using the safety population. The most severe grade per patient will be reported. Elapsed days of toxicity will be summarized with descriptive statistics. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent adverse events will be presented in tabular form.

9.4.5. BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be presented to characterize the patient population. No inferential statistics will be conducted since this is a single site, one-arm trial.

9.4.6. PLANNED INTERIM ANALYSES

Interim analyses will be performed during the phase 1 portion to assess dose limiting toxicity and to confirm escalation rules. A final interim analysis will be performed on dose limiting data to confirm the recommended phase 2 dose. An interim analysis is not planned on the phase 2 expansion.

9.4.7. SUB-GROUP ANALYSES

No subgroup analyses will be conducted.

9.4.8. TABULATION OF INDIVIDUAL PARTICIPANT DATA

This protocol will comply with section 2038 of the 21st Century Cures Act and supply participant level data as required. De-identified individual-level participant data will be supplied for:

- Gender (self-declared by participant)
- Race
- Ethnicity
- Age at enrollment (in years)

These data will be provided as required in the NIH progress reports.

9.4.9. EXPLORATORY ANALYSES

Mixed effects regression models will be utilized to estimate changes in patient reported outcome measures (PROM), and tumor infiltrating and peripheral T lymphocytes. Random effects will be included to account for the longitudinally correlated nature of repeated measurements. Graphical plots of the estimated mean and associated 95% confidence intervals by time point in the study will be produced.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1.INFORMED CONSENT PROCESS

Elements of Consent
All elements as required under Federal law will be included in the informed consent document. No elements will be waived. Consent forms will be IRB approved.

Assent
Assent will not be used.

Legally authorized representative
To comply with ICH Good Clinical Practice (E6 R2), those who cannot provide independent consent will not be included, as the research goals can be met apart from this population.

Translation(s)
Translated documents and interpreters will not be used for this trial.

Consent/assent and Other Informational Documents Provided to participants
Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

Consent Procedures and Documentation
Consent is obtained from those authorized in the research team (as listed in the approved IRB application and/or delegation of authority log). The consent discussion will take place in a private examination or consult room in the clinic or in the patient's room on the inpatient unit. The potential study participant is provided as much time as needed to review the consent document before a response is required and is encouraged to take the document home for review. Additional copies are provided for family, caregivers, and/or friends as appropriate. Contact information for the research team (typically, the principal investigator, the treating physician(s), and the research nurse(s)) is provided for follow-up questions.

The consenting party asks for full understanding by the potential subject throughout the consent process. The consenter asks the potential subject if there are any questions during the oral description of the study and asks for verbal acknowledgement of full understanding of the study procedures and the general consent elements after a thorough oral presentation of the consent document and after the subject has had time to read it fully and discuss with relatives and friends if desired. The consenter will not attempt to obtain consent if there is any inclination of reduced cognitive ability or concerns of a relative or friend regarding the subject's ability to give consent to the study procedures.

Both the participant and the consenting party will sign the informed consent document consistent with local and Federal requirements. A copy of the signed informed consent document will be provided to the participant. The original signed document will be stored as source document in the participant's case history.

10.1.2.STUDY DISCONTINUATION AND CLOSURE

When a study is prematurely terminated, refer to Section **7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal**, for handling of enrolled study participants.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, the investigator, the funding agency, the Center for Drug Evaluation and Research (CDER) of FDA, the IRB(s) of record, and the Data and Safety Monitoring Committee (DSMC) overseeing this study. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

For procedures if the study is halted or prematurely terminated, please refer to Protocol 6.7 as a guideline for safety procedures and final data collection.

10.1.3.CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Iowa's Holden Comprehensive Cancer Center using the clinical trials management system OnCore™ (Forte Research Systems, Madison WI). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Iowa.

10.1.4.FUTURE USE OF STORED SPECIMENS AND DATA

Participants have the option to permit their medical images, blood and tumor tissue to be stored for future use and to be shared with other researchers. A tracking log is utilized to track those participants who opt-in.

Data collected for this study will be analyzed and stored at the University of Iowa (Iowa City, IA). After the study is completed, for those participants who opted-in to archiving their information, data will be de-identified and archived at the University of Iowa. Researchers interested in using these data will be required to sign a data-use agreement, which limits further secondary analysis as per the Revised Common Rule (January, 2018).

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the University of Iowa with the same goal. These samples could be used to research the causes of cancer, its complications and other conditions for which individuals with genetic mutations are at increased risk, and to improve treatment. The University of Iowa will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

The individual participant can choose to withdraw consent to have biological specimens stored for future research at any time. If research with the blood, tissue, or medical imaging has already been completed, the information from that research may still be used.

10.1.5.KEY ROLES AND STUDY GOVERNANCE

Sponsor-Investigator, IND exemption 158036	Biostatistician	Regulatory Manager
Joseph Caster, Ph.D., M.D.	Sarah Bell, M.S.	Kellie Bodeker, MSHS, Ph.D., CCRC
Department of Radiation Oncology	Holden Comprehensive Cancer Center	Department of Radiation Oncology
The University of Iowa	The University of Iowa	The University of Iowa
200 Hawkins Drive, Iowa City IA	200 Hawkins Drive, Iowa City IA	200 Hawkins Drive, Iowa City IA
319.353.8836	(319) 217-0376	(319) 384-9425
joseph-caster@uiowa.edu	sarah-mott@uiowa.edu	kellie-bodeker@uiowa.edu

10.1.6.SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Committee (DSMC) composed of individuals with the appropriate expertise. A current roster is available on-line at **https://uihc.org/data-and-safety-monitoring-committee**. This committee's membership and policies have been reviewed and approved by the National Cancer Institute under the Holden Comprehensive Cancer Center's Cancer Center Support Grant and Comprehensive Cancer Center designation. Members of the DSMC should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. For this reason, an independent reviewer has been designated for this study (William McGinnis, MD). The DSMC will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSC operate under the rules of the NCI-approved charter. Key & critical data elements the DSMC have been clearly defined and are provided (10.1.8). The DSMC will provide its input to the IND Sponsor, the IND medical monitor and – as appropriate – the IRB of record, the FDA, the NCI, and/or the responsible funding agency.

10.1.7.CLINICAL MONITORING: HOLDEN COMPREHENSIVE CANCER CENTER DSMC

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the Holden Comprehensive Cancer Center's Data and Safety Monitoring Committee per the approved, filed plan with the National Cancer Institute.
- The trial's research records will be monitored at minimum twice per year with a minimum of 25% of subjects monitored for the entire study participation (from enrollment to completion of study intervention).
- The investigator will be provided copies of monitoring reports within 14 days of visit / review.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP) on file with the Holden Comprehensive Cancer Center. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits will be conducted by the DSMC's designee or the sponsor's designee to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10.1.8. IND EXEMPTION 158036 (J. CASTER, SPONSOR) MONITORING AND COMPLIANCE PLAN

21 CFR 312.56 requires the IND sponsor to monitor progress of all ongoing investigations conducted under that sponsor's IND; an exemption is not made for INDs held by research investigators. Reviewing FDA warning letters to investigator-sponsors, the most common finding (> 90%) is monitoring compliant with the FDA's expectations. To address this issue, the following DSMP is on file with this IND for this clinical trial.

As an independent research trial under an investigator-sponsored IND, the sponsor has approved the following individualized monitoring plan to fulfill the requirements set forth in 21 CFR§312.50 and §312.56 in addition to ICH E6 and the FDA Bioresearch Monitoring Program's Compliance Program Guidance Manual CPGM 7348.811.

The following plan was developed after reviewing the F*DA's Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013), the *NIH guidance OD-00-038 Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials*, the NCI's *Conducting Clinical Trials: Essential Elements*, and the International Conference on Harmonisation *E6: Guideline for Good Clinical Practice*, which has been listed by the FDA in the Federal Register as an accredited guidance document.

Per the FDA (August, 2013) sponsors are encouraged to "…tailor monitoring plans to the needs of the trial." The FDA also places greater emphasis on centralized monitoring than the ICH E6 document, citing that centralized monitoring as described by the FDA (August 2013) was not yet feasible when the E6 document was completed.

Centralized Monitoring (CM)
For the purposes of this study, centralized monitoring refers to timely and accurate data entry into a spreadsheet for review by the principal investigator, sponsor, and/or designee. Remote monitoring enables data to be evaluated for quality, safety, and an interim analysis in real-time. Data to be entered are those identified as critical by the principal investigator and sponsor. Critical data can be monitored remotely through centralized monitoring (FDA, 2013, page 11).

CM — critical data

- Eligibility criteria (lab values, performance status, date of results)
- Baseline constitutional assessments performed and graded (Y/N)
- CBC w/diff ordered at protocol time points and reviewed (Y/N)
- Comprehensive metabolic panel ordered at protocol time points and reviewed (Y/N)
- Constitutional assessments performed and graded per protocol (Y/N)
- List of adverse events, with CTCAE grading, collected from initial infusion to +24 weeks after the last study infusion with codified attribution (if SAE or ≥ grade 3).

CM — frequency of entry and review

Centralized data will be entered within 2 weeks of the infusion. Data will be reviewed no less than quarterly by the PI, sponsor, or designee. Email or written documentation of review will be sent to the sponsor or the sponsor's designee. Alternatively, review can be performed or confirmed at sponsor-directed IND meetings.

On-Site Monitoring (On-Site)
Additional monitoring may be ordered by the principal investigator or sponsor. The principal investigator may select the monitor for the study but final approval must be obtained from the sponsor prior to any monitoring activities.

On-Site— critical data
At minimum, the outside monitor will review the protocol against the provided monitoring sheet. Additional data to be reviewed may be added at the request of the sponsor, the sponsor's designee, the principal investigator, or the principal investigator's designee.

On-Site — frequency of review
Frequency of review (in addition to the monitoring provided by the HCCC monitoring plan) will be determined by quality audits performed by the sponsor or sponsor's designee.

On-Site — reports
Monitoring reports will comply with ICH *E6* and the FDA's *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013). Finalized reports will be submitted to the sponsor, the principal investigator, the principal investigator's designee, and the sponsor's designee within 30 calendar days of the on-site monitoring visit. A copy of the final report, and any corrective action plans, will be submitted to the institutional review board.

On-Site — BIMO
If directed, monitoring complying with the FDA's Biomedical Research Monitoring Compliance Program (CPM 7348.811, part III) will be completed. This inspectional guide outlines monitoring deemed by the FDA as necessary when seeking a New Drug Approval. This compliance program manual is available on-line:

http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133569.htm

To prepare for a BIMO inspection, and to again verify the trial is being monitored effectively, the research team is required to maintain a binder compliant with these inspectional requirements (items C – H, J)

10.1.9. QUALITY ASSURANCE AND QUALITY CONTROL

> The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.
>
> To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.
>
> ~ International Conference on Harmonisation, *E6*

The sponsor intends to comply with auditing procedures to evaluate conduct and compliance with protocol, SOPs, GCP, and the DSMP filed with this protocol. Audit findings will be disseminated and discussed at quality meetings by the sponsor.

10.1.10. DATA HANDLING AND RECORD KEEPING

10.1.10.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. All source documents should meet the FDA standard of ALCOA (attributable, legible, contemporaneous, original, and accurate).

Source document worksheets will be used for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. The study site's electronic medical records, including radiation verify and record systems, will mined for data. The EMR will be considered prime source.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into OnCore™ (Forte Research Systems, Madison WI), a 21 CFR Part 11-compliant data capture system provided by The University of Iowa Holden Comprehensive Cancer Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents and monitored to verify against transcription errors.

10.1.10.2. STUDY RECORDS RETENTION

As a study conducted under an investigational new drug application study records must be maintained until the IND sponsor notifies the investigator in writing that they may be destroyed.

The study site must verify with the IRB of record, and any other Federal and local policies, prior to destroying the study records.

10.1.11. PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and record deviations within 2 working days of identification of the protocol deviation. A protocol violation – a deviation resulting in harm or increased risk to the subject (or decreased acceptability of risk) must be reported to the IND sponsor within 1 working day. All deviations must be addressed in study source documents. Deviation logs must be provided annually to the IND sponsor. Protocol deviations and violations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.12. PUBLICATION AND DATA SHARING POLICY

This study is registered on clincialtrials.gov Results will be posted as required by FDAAA 801. Other data sharing, such as archived de-identified datasets, will be shared with other researchers after a data-sharing agreement has been signed.

Publications, including peer-reviewed publications, will be submitted in compliance with ICMJE's requirements. Any publications or presentations will provide only de-identified data to safeguard participant privacy>

10.1.13. CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with The University of Iowa has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.]

10.2. ADDITIONAL CONSIDERATIONS

None.

10.3. ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4. PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.0	27 Aug 2021	IND exemption number added	Exemption deemed by FDA CDER
Initial draft submitted to IRB			
2.0	07 Oct 2021	Statistics revised	PRMC review
3.0	14 Dec 2021	Housekeeping errors	PRMC review
4.0	01 Apr 2022	Global modifications as per SOC	Changes to accommodate clinic
5.0	01 Jul 2023	Revision to accommodate change in SOC to TNT; statistics revised	Aligns with new national SOC

Version 4.0	**28 March 2022**	
Title page	Updates to version, date	Housekeeping
TOC	Updated table of contents	Housekeeping
1.3 SOA	Surgery window extended through W16	Accommodate pandemic impact on schedules
	Physical exam specified to be within 7 days of day 1	Accommodate clinical schedules for evaluation of prescription(s)
	Physical exam prior to surgery	With extension of surgical window, clarify that the physical exam takes place prior to surgery for surgical clearance.
	Pregnancy test shifted to be within 72h of day 1 dosing of niraparib	GSK recommendation. Participant must confirm on highly effective birth control.
	Pregnancy test ordered during each infusion	GSK recommendation.
	CMP performed during RT week	Clarification
	CMP to be done within 72h of infusion	Accommodate draws prior to Monday infusions
	CMP to be done prior to surgery	Harmonize to the physical exam for surgical clearance
	CBC w/diff to be within 7 days of day 1	Harmonize to the physical exam
	CBC w/diff weekly during study treatment	Aligned text to be within study treatment columns
	CBC w/diff prior to surgery	Harmonize to the physical exam for surgical clearance
	Thyroid panel begins 4 weeks after D1…	Aligned text to be within study treatment columns
	Urinalysis to be within 7 days of day 1	Harmonize to the physical exam
	Urinalysis: specified W16 & 21	Typographical error; meant to be assessed at discrete points
	CD4/CD8 lymphocytes ≤ 7d last niraparib dose	Assessment is to be completed after final dose
	ECG to be obtained prior to surgery	Intended to be pre-surgical assessment
	Dostarlimab infusion(s) changed to weeks	Provide flexibility in scheduling.
	Vital signs are obtained within 7 days of day 1	Harmonize to the physical exam
	Sigmoidoscopy changed to Scope	Anoscopy and colonoscopy are also allowed.
	Solicited Adverse Events changed to Adverse Events	Both solicited and unsolicited AEs are collected at these timepoints.
	Adverse events	Harmonized to protocol text
	Assess for MDS/AML within 7 days of day 1	Harmonized to the physical exam
	Footnotes	Provided detail on additions and changes
6.1.2.1.1	Deleted, “treatment emergent toxicity leading to a delay of > 28 days in initiating C2 therapy,” and replaced with, “A treatment emergent toxicity that, in the opinion of the study investigator, is clinically significant and would preclude further treatment (i.e., dose limiting toxicity).”	This was felt to be more appropriate given the complexities of determining dose modifications, delays, and participant tolerance.

6.1.2.1.1	Inserted, “of planned,” to surgery toxicity	To clarify given the increased window for surgery due to the pandemic.
6.1.2.1.3	Inserted, “missed doses will not be made up.”	Clarification.
6.1.2.1.3	Deleted, “Dose modifications and delays are not allowed for the phase 1b portion of the trial.”	A dose limiting toxicity was defined as a delay in > 28 days of therapy. This was circular logic. This was deleted and the qualification in 6.1.2.1.1 added.
Table 2.	Deleted “Phase 2”	Dose modifications for 200 mg niraparib cohort may be employed.
Table 3.	Deleted “Phase 2”	Dose modifications for 200 mg niraparib cohort may be employed.
Table 3.	Platelet count < 100,000 / uL: inserted, “or if original prescription is 100 mg dose.”	Clarification that dose modifications are not performed for doses starting at 100 mg.
6.1.2.2.	Deleted, “Dose modifications and delays are not allowed for the phase 1b portion of the trial.”	A dose limiting toxicity was defined as a delay in > 28 days of therapy. This was circular logic. This was deleted and the qualification in 6.1.2.1.1 added.
8.1.1	Clarified mutation analysis and TIL are exempted from window	Not time sensitive
8.2.2	ECG and PT/INR deleted from baseline	Not included in baseline; SCR only.
8.2.3	Deleted “weekly” for adverse events	Error; schedule provided within the text.
8.2.3	CBC w/diff edited to harmonize with SOA	CBC with are drawn weekly after initiating niraparib; does not have to be done day 1.
8.2.3	CMP edited to harmonize with SOA.	Typographical error.
8.2.3	72 hour window allowed for CMP	To allow blood to be obtained Friday for a Monday physical exam / infusion.
12.1	Radiation therapy starts on day 8	Typographical error.
Version 3.0: 14 December 2021		
Title page	Updates to version, date	Housekeeping
TOC	Updated table of contents	Housekeeping
Throughout	Corrected spelling errors	Housekeeping
6.1.2.1.1	Corrected “3 x 3” to “3+3”	Housekeeping
8.3.7	Deleted SAE table	Per PRMC determination
Version 2.0: 07 September 2021		
Title page	Updates to version, date	Housekeeping
TOC	Updated table of contents	Housekeeping
1.1	Updated synopsis to align with statistics	Housekeeping
3.0	Updated to align with statistics	Housekeeping
4.1	Updated to align with statistics	Housekeeping
5.3	Updated to align with statistics	Housekeeping
9.0	Updated hypotheses and analyses	As per statistician of record
Version 1.0: 27 August 2021		
Title page	Updates to version, date	Housekeeping; version 1.0 signifies active version
TOC	Updated table of contents	Housekeeping
SOA	Inserted CRT, ALT, AST, TBIL at screening	Housekeeping; align with eligibility criteria
SOA	Inserted PT/PTT/INR	Housekeeping; align with eligibility criteria
SOA	Marked CBC W/diff at SCR	Housekeeping; align with eligibility criteria
5.1.2	Inserted line break for HIV vs. hepatitis; renumbered accordingly	Deleted in error
6.1.1.1	Inserted IND exemption number	Deemed exempt by FDA CDER
6.1.1.2	Inserted IND exemption number	Deemed exempt by FDA CDER
10.1.5	Inserted IND exemption number	Deemed exempt by FDA CDER
10.1.8	Inserted IND exemption number	Deemed exempt by FDA CDER
Header	Updated version and date	Housekeeping
Header	Inserted TOPAZ study acronym	Housekeeping

11. REFERENCES

1. Seyedin SN, Hasibuzzaman MM, Pham V, et al. Combination Therapy with Radiation and PARP Inhibition Enhances Responsiveness to Anti-PD-1 Therapy in Colorectal Tumor Models. *Int J Radiat Oncol Biol Phys.* 2020;108(1):81-92.

2. Duska LR, Scalici JM, Temkin SM, et al. Results of an early safety analysis of a study of the combination of pembrolizumab and pelvic chemoradiation in locally advanced cervical cancer. *Cancer.* 2020;126(22):4948-4956.

3. George TJ, Yothers G, Hong TS, et al. NRG-GI002: A phase II clinical trial platform using total neoadjuvant therapy (TNT) in locally advanced rectal cancer (LARC)—First experimental arm (EA) initial results. *Journal of Clinical Oncology.* 2019;37(15_suppl):3505-3505.

4. Joshi M, Tuanquin L, Kaag M, et al. Concurrent durvalumab and radiation therapy followed by adjuvant durvalumab in patients with locally advanced urothelial cancer of bladder (DUART): Btcrc-GU15-023. *Journal of Clinical Oncology.* 2020;38(6_suppl):513-513.

5. Rahma OE, Yothers G, Hong TS, et al. NRG-GI002: A phase II clinical trial platform using total neoadjuvant therapy (TNT) in locally advanced rectal cancer (LARC)—Pembrolizumab experimental arm (EA) primary results. *Journal of Clinical Oncology.* 2021;39(3_suppl):8-8.

6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Rectal cancer v1.2021. *https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf*. Published 2020. Updated 22 December. Accessed 10 March, 2021.

7. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med.* 2006;355(11):1114-1123.

8. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004;351(17):1731-1740.

9. Bryant CL, Lunniss PJ, Knowles CH, Thaha MA, Chan CL. Anterior resection syndrome. *The Lancet Oncology.* 2012;13(9):e403-408.

10. Juul T, Ahlberg M, Biondo S, et al. Low anterior resection syndrome and quality of life: an international multicenter study. *Diseases of the colon and rectum.* 2014;57(5):585-591.

11. NRG Oncology. NCT02921256: NRG GI002 - Veliparib, Pembrolizumab, and Combination Chemotherapy in Treating Patient With Locally Advanced Rectal Cancer. *https://clinicaltrials.gov/ct2/show/NCT02921256*. Published 2021. Updated 25 February. Accessed 10 March, 2021.

12. Valentini AM, Di Pinto F, Cariola F, et al. PD-L1 expression in colorectal cancer defines three subsets of tumor immune microenvironments. *Oncotarget.* 2018;9(9):8584-8596.

13. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med.* 2015;372(26):2509-2520.

14. Li Y, Liang L, Dai W, et al. Prognostic impact of programed cell death-1 (PD-1) and PD-ligand 1 (PD-L1) expression in cancer cells and tumor infiltrating lymphocytes in colorectal cancer. *Mol Cancer.* 2016;15(1):55.

15. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *The Lancet Oncology.* 2017;18(9):1182-1191.

16. Aguilera TA, Rafat M, Castellini L, et al. Reprogramming the immunological microenvironment through radiation and targeting Axl. *Nat Commun.* 2016;7:13898.

17. Filatenkov A, Baker J, Mueller AM, et al. Ablative Tumor Radiation Can Change the Tumor Immune Cell Microenvironment to Induce Durable Complete Remissions. *Clin Cancer Res.* 2015;21(16):3727-3739.

18. Formenti SC, Rudqvist NP, Golden E, et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. *Nat Med.* 2018;24(12):1845-1851.

19. Reits EA, Hodge JW, Herberts CA, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med.* 2006;203(5):1259-1271.

20. Sato H, Niimi A, Yasuhara T, et al. DNA double-strand break repair pathway regulates PD-L1 expression in cancer cells. *Nat Commun.* 2017;8(1):1751.

21. Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen. *Cancer Immunol Res.* 2015;3(4):345-355.

22. Huang J, Wang L, Cong Z, et al. The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a Brca1(-/-) murine model of ovarian cancer. *Biochem Biophys Res Commun.* 2015;463(4):551-556.

23. Jiao S, Xia W, Yamaguchi H, et al. PARP Inhibitor Upregulates PD-L1 Expression and Enhances Cancer-Associated Immunosuppression. *Clin Cancer Res.* 2017;23(14):3711-3720.

24. Kim K, Skora AD, Li Z, et al. Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells. *Proc Natl Acad Sci U S A.* 2014;111(32):11774-11779.

25. Konstantinopoulos PA, Waggoner S, Vidal GA, et al. Single-Arm Phases 1 and 2 Trial of Niraparib in Combination With Pembrolizumab in Patients With Recurrent Platinum-Resistant Ovarian Carcinoma. *JAMA Oncol.* 2019.

26. Vinayak S, Tolaney SM, Schwartzberg L, et al. Open-Label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer. *JAMA Oncol.* 2019.

27. Lesueur P, Chevalier F, El-Habr EA, et al. Radiosensitization Effect of Talazoparib, a Parp Inhibitor, on Glioblastoma Stem Cells Exposed to Low and High Linear Energy Transfer Radiation. *Sci Rep.* 2018;8(1):3664.

28. Tuli R, Surmak AJ, Reyes J, et al. Radiosensitization of Pancreatic Cancer Cells In Vitro and In Vivo through Poly (ADP-ribose) Polymerase Inhibition with ABT-888. *Transl Oncol.* 2014.

29. Hussain MH, Glass TR, Forman J, et al. Combination cisplatin, 5-fluorouracil and radiation therapy for locally advanced unresectable or medically unfit bladder cancer cases: a Southwest Oncology Group Study. *J Urol.* 2001;165(1):56-60; discussion 60-51.

30. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med.* 2012;366(16):1477-1488.

31. Perdona S, Autorino R, Damiano R, et al. Bladder-sparing, combined-modality approach for muscle-invasive bladder cancer: a multi-institutional, long-term experience. *Cancer.* 2008;112(1):75-83.

32. Tree AC, Jones K, Hafeez S, et al. Dose-limiting Urinary Toxicity With Pembrolizumab Combined With Weekly Hypofractionated Radiation Therapy in Bladder Cancer. *Int J Radiat Oncol Biol Phys.* 2018;101(5):1168-1171.

33. Royal Marsden NHS Foundation Trust. NCT02560636: Pembrolizumab in Muscle Invasive/Metastatic Bladder Cancer (PLUMMB). *https://clinicaltrials.gov/ct2/show/NCT02560636*. Published 2020. Updated 07 April. Accessed 10 March, 2021.

34. U.S. Food and Drug Administration (FDA). Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics. *https://www.fda.gov/media/71195/download*. Published 2018. Updated December. Accessed 30 August, 2022.

35. Bailey DG, Dresser G, Arnold JM. Grapefruit-medication interactions: forbidden fruit or avoidable consequences? *CMAJ.* 2013;185(4):309-316.

36. Costa R, Carneiro BA, Agulnik M, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. *Oncotarget.* 2017;8(5):8910-8920.

37. U.S. Food and Drug Administration (FDA). Safety Assessment for IND Safety Reporting: Guidance for industry. *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM477584.pdf*. Published 2015. Updated December. Accessed 10 January, 2018.

12. APPENDIX A: RADIATION THERAPY GUIDELINES

12.1. RADIATION THERAPY

This radiation therapy technique is an accepted national standard of care practice for the treatment of this cancer. Participants will undergo CT simulation following national standards. If available, FDG PET/CT imaging will be imported to aid in identifying gross tumor. Regions of interest will be contoured on CT images and, if available, PET images. Radiation planning and dose calculations will be performed using commercial treatment planning software (Pinnacle v.9.8, Philips, Fitchburg, WI). Participants will be treated with intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) to minimize mean dose to femoral, pelvic, and lumbar bone marrow. The entire mesorectum will be treated to a total dose of 25 Gy. Participants will receive 5 Gy per fraction, one fraction per day, for 5 consecutive days. Radiation therapy begins on study day 8. In order to minimize hematologic toxicity, the following dose/volume objectives for femoral, pelvic, and lumbar bone marrow will be utilized: V5 (volume receiving 5 Gy) < 95%, V12.5 < 45%, Iliac crest Dm (mean dose) < 17 Gy.