NRG ONCOLOGY

NRG-GI002

(ClinicalTrials.gov NCT02921256)

A Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy (TNT) in Rectal Cancer

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: ALLIANCE/Alliance for Clinical Trials in Oncology, ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, NRG/NRG Oncology, and SWOG/SWOG.

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NRG ONCOLOGY
NRG-GI002

A Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy (TNT) in Rectal Cancer

Protocol Agents

Agent	Supply	NSC #	IND #	IND Sponsor
Capecitabine	Commercial	712807	131922	DCTD, NCI
Oxaliplatin	Commercial	266046		
5-Fluorouracil	Commercial	19893		
Leucovorin	Commercial	3590		
Veliparib (ABT-888)	Investigational	737664		
MK-3475 (Pembrolizumab)	Investigational	776864		

Participating Sites

☒ U.S.

☐ Canada

☐ Approved International Member Sites

Document History

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Amendment 5	February 20, 2020
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Amendment 3	June 4, 2019
Amendment 2	June 25, 2018
Amendment 1	June 15, 2018
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Original	May 31, 2016

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance. **For detailed information on the regulatory and monitoring procedures for CTSU sites**, please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU Member website at https://www.ctsu.org >resources tab> CTSU Operations Information.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN), which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave®. Please see the data submission section of the protocol for further instructions Do NOT submit study data or forms to CTSU Data Operations. Do NOT copy the CTSU on data submission.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member website located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e., patient eligibility or treatment-related), contact the Clinical Coordinating Department at NRG Oncology at 1-800-477-7227 or by e-mail at ccdPGH@nrgoncology.org		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission), contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923 or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. **For data submission questions**, contact the GI002 Data Manager at the NRG Oncology Statistics and Data Management Center by calling 412-624-2666. **For detailed information on the regulatory and monitoring procedures for CTSU sites**, please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU Member website at https://www.ctsu.org >resources tab> CTSU Operations Information.		
The CTSU website is located at https://www.ctsu.org.		

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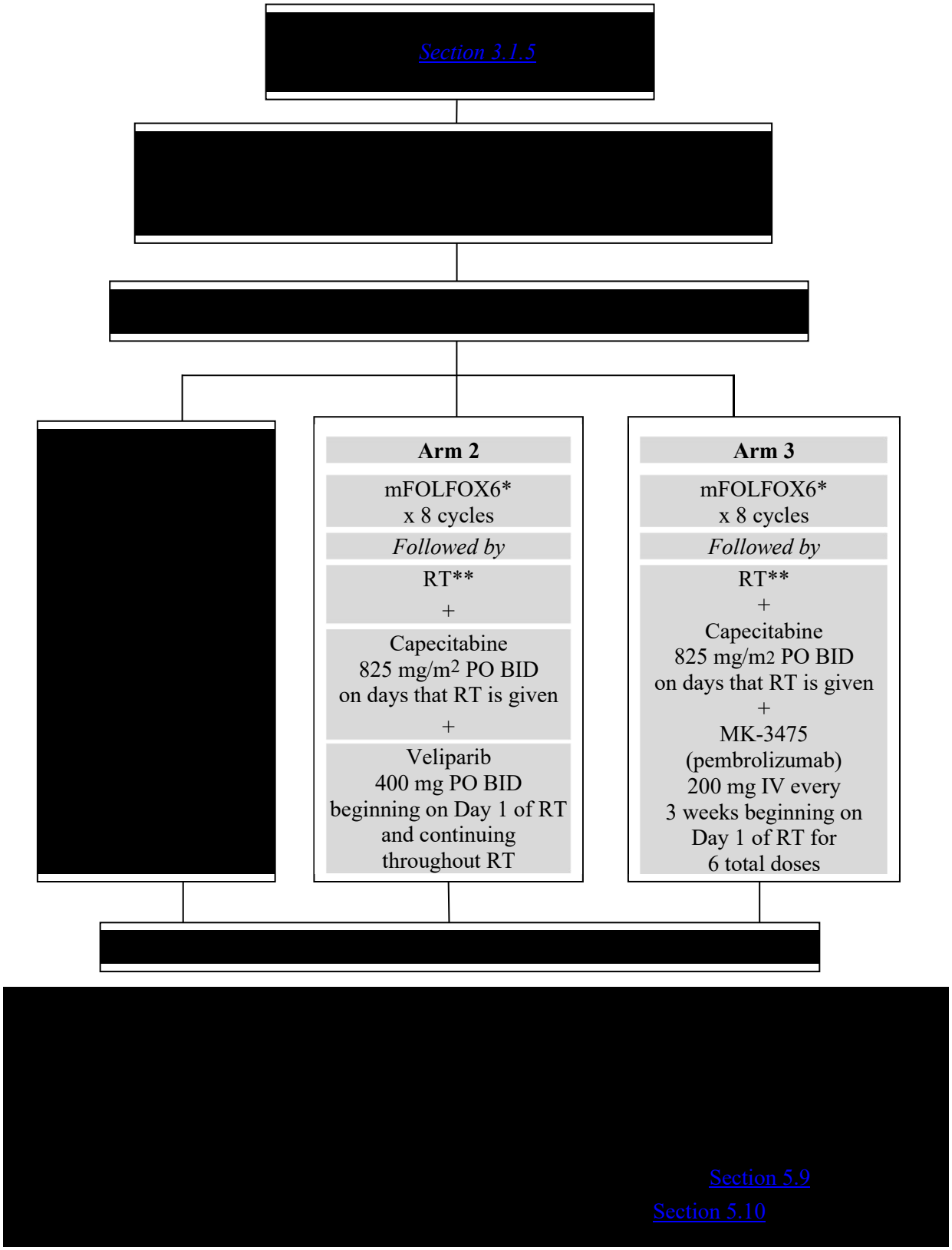
Figure 1. NRG-GI002 SCHEMA

Note: Arm 2 was closed to accrual on February 12, 2018 and Arm 3 was closed to accrual on May 13, 2019 which is indicated by the light gray shaded box.



1.0 OBJECTIVES

1.1 Primary Objective

To demonstrate an absolute improvement in Neoadjuvant Rectal Cancer (NAR) score for the experimental regimen as compared to concurrently randomized control patients.

1.2 Secondary Objectives

1.2.1 To compare overall survival (OS)

1.2.2 To compare disease-free survival (DFS)

1.2.3 To compare the rate of pathologic complete response (nodes and tumor)
Pathologic response to preoperative therapy will be determined at the time of surgical resection. Pathologic complete response (pCR) is defined as no evidence of invasive tumor cells on pathologic examination of the primary rectal cancer (or tissue from the area where the tumor had been if there is a complete clinical response).

1.2.4 To compare the rate of sphincter preservation

1.3 Tertiary Objectives

1.3.1 To compare the proportion of patients who have a tumor resection overall, conditional on beginning induction chemotherapy, and conditional on beginning chemoradiotherapy

1.3.2 To compare time from initiation of chemoradiotherapy to surgery in the subset of patients with tumor resection

1.4 Exploratory Objectives

1.4.1 To estimate the rate of disease progression during chemotherapy (prior to chemoradiation)

1.4.2 To compare the rate of clinical complete response rate (cCR)
Presence or absence of complete clinical response will be assessed immediately prior to surgery by perioperative digital rectal exam and either sigmoidoscopy or proctoscopy. Clinical complete response (cCR) is defined as no visible or palpable rectal primary tumor.

1.4.3 To compare the rate of negative circumferential margin

1.4.4 To compare the rate of completion of all cycles of neoadjuvant chemotherapy

1.4.5 To compare the rate of completion of full course of chemoradiation

1.4.6 To compare the toxicity and safety between interventions

1.4.7 To explore the correlative molecular predictors of response and distant failure

1.4.8 To explore the relationship between radiographic findings and pathologic outcomes

2.0 BACKGROUND

2.1 Introduction

Multiple attempts to improve outcomes in rectal cancer through enhancement of radiosensitization by adding agents such as oxaliplatin to 5-FU have demonstrated no clinical benefit but added toxicity (O'Connell 2014; Aschele 2011; Gérard 2012). However, there is a strong preclinical rationale as well as limited clinical studies supporting the hypothesis of radiosensitization. Additionally, 25-70% of patients treated with neoadjuvant chemoradiotherapy and surgery fail to obtain appropriate adjuvant systemic chemotherapy (O'Connell 2014; Khrizman 2013; Roh 2009; Sauer 2004). This proposed study is a randomized phase II platform with parallel, non-comparative experimental arms in locally advanced and high-risk rectal cancer. It will provide a systematic approach to study novel radiosensitizers, personalized treatment selection using novel targeted systemic therapeutics and identify patients at exceptionally high risk for recurrence. Thus, the TNT protocol provides the basis for more definitive randomized controlled studies after demonstration of substantive activity.

This trial platform holds the promise of rapidly and prospectively determining the worth of novel radiosensitizers, novel systemic therapies or other therapeutic interventions in the setting of locally advanced rectal adenocarcinoma. Development of more potent radiosensitizers in rectal cancer represents a scientific strategy with important clinical significance vis a vis patients with advanced pelvic disease who may benefit from more effective local control, those with earlier stage disease who may benefit from non-surgical or less radical interventions and a greater likelihood of organ (sphincter) preservation. Likewise, testing of novel systemic therapy interventions in this population allows for demonstration of in vivo response, correlative biomarker refinement, and identification of potential mechanisms of resistance.

Rectal cancer represents a tumor type that allows serial biopsies during clinical care without significant risk to the patient. This affords an opportunity for scientific discovery, correlating clinical outcomes with molecular and biomarker interrogation.

2.2 Neoadjuvant Rectal Cancer (NAR) Score

Yothers, et al developed the Neoadjuvant Rectal Cancer (NAR) score as a short term clinical trial surrogate endpoint to take variables associated with treatment effect beyond pCR into consideration (Yothers 2014; George 2015). This composite score was built upon the Valentini nomogram as a research tool to predict local recurrence, distant metastases and overall survival for patients with locally advanced rectal cancer treated with neoadjuvant therapy (Valentini 2011). The NAR score is based upon the degree of downstaging noted between the initial cT/pT and pN positivity and was validated in NSABP R-04. By using variables commonly available in rectal cancer neoadjuvant clinical trials, it was proven to predict recurrence free and overall survival more accurately than pCR. This surrogate clinical trial endpoint was subsequently independently and externally validated in an international dataset providing further evidence of utility as a short term surrogate (Raissouni 2014). A detailed analysis of NAR scores was also undertaken in several studies to confirm the appropriateness of this surrogate in trials which incorporate neoadjuvant systemic therapy. In the CONTRE and GCR3 (induction arm) studies (Perez 2014; Fernandez-Martos 2015), the NAR score performed similar to that of NSABP R-04, including in the subsets of patients with locally advanced or low lying tumors that would otherwise be eligible for this protocol (Yothers personal communication).

2.3 Current Arms, Future Intent

The intent of this study is to serve as a platform to test novel agents or hypotheses in neoadjuvant treatment of rectal cancer. Additional experimental arms will be considered through protocol amendments after formal review including information specific to that arm as well as a statistical plan for control arm comparison. Success of any given experimental arm will be determined by achievement of pathologic endpoints included in the NAR score reduction supporting a higher likelihood of success in subsequent definitive randomized controlled studies.

2.3.1 RT + capecitabine (Arm 1/control arm)

Fluoropyrimidine therapy concurrent with radiotherapy for rectal cancer currently represents the standard of care for this disease (NCCN Guidelines [Rectal Cancer] 2014). The Gastrointestinal Tumor Study Group showed that adjuvant combined modality therapy with radiotherapy and 5-fluorouracil (5-FU)-based chemotherapy improved outcomes in patients with rectal cancer both in terms of local control and overall survival compared to postoperative radiotherapy alone (Krook 1991). The incorporation of protracted infusional 5-FU with radiotherapy further improved clinical outcomes (O'Connell 1994). NSABP R-04 demonstrated similar clinical outcomes between capecitabine and continuous infusion 5-FU when added to radiotherapy for rectal cancer. Pathologic complete responses were similar between the two arms (22.2 vs 18.8%; p=0.12) while toxicity clinically favored capecitabine (O'Connell 2014). This control arm is included to provide contextual and contemporary reference for the experimental arms and biomarker substudies. It will also facilitate secondary validation of the NAR score as a surrogate for survival in patients treated with trimodality therapy in a completely neoadjuvant fashion.

2.3.2 RT + capecitabine + veliparib (Arm 2)

As DNA is continually damaged, it is repaired by a distinct integrated network of DNA repair mechanisms. Double-stranded DNA breaks, which typically occur with radiation, (Takahashi 2005) recruit homologous recombination and non-homologous end-joining pathways to repair these double-strand breaks. Single-strand breaks utilize another pathway including nucleotide-excision repair, base-excision repair and mismatch repair. Poly(ADP-ribose) polymerase (PARP) is a nuclear enzyme that rapidly recognizes and binds to single strand breaks and facilitates single strand DNA repair. Since there are at least two sets of mechanisms leading to DNA repair, the disruption of one pathway may not lead to cell death; however, when both pathways are disrupted the accumulated genomic instability leads to loss of viability. This concept, known as synthetic lethality, is supported by clinical studies in BRCA deficient cancers and triple negative breast cancer (O'Shaughnessy 2011; Fong P 2009). In preclinical studies, it has been observed that PARP knock-out mice develop normally but exhibit an extreme sensitivity to high doses of gamma-radiation. This observation suggests that specific inhibition of PARP would sensitize cells to radiation and be non-toxic to unirradiated tissues (de Murcia 1997). Using cell lines and a clonogenic survival assay, PARP-1 inhibitors have been shown to enhance the efficacy of radiotherapy regimens by interfering with DNA repair mechanisms (Chalmers 2004; Brock 2004). Veliparib (ABT-888) in combination with radiation in HCT-116 colon carcinoma xenograft model showed a near doubling in median survival compared to radiation alone while ABT-888 alone was no better than vehicle (Donawho 2007). A similar synergistic effect was demonstrated when veliparib was combined with 5-FU and RT compared to 5FU and RT alone in preclinical colorectal cancer xenograft models (Shelton 2013).

In a first phase 0 trial of its kind in oncology drug development, 13 patients with advanced malignancies received veliparib and demonstrated good oral bioavailability and statistically

significant inhibition of poly (ADP-ribose) levels in tumor biopsies and peripheral blood mononuclear cells at 25 mg and 50 mg dose levels. Greater than 90% inhibition of PAR (poly [ADP-ribose]) levels was observed 3 to 6 hours post-drug administration, with recovery at 24 hours in both xenograft models and in the clinical trial. A single dose of veliparib resulted in significant inhibition of PAR in tumor biopsies. This suggests a twice-daily schedule for veliparib administration to be ideal (Kummar 2009). There are a number of ongoing phase I and II studies with veliparib either alone or in combination with chemotherapy. However, a recently reported phase I study testing the safety and tolerability of veliparib with capecitabine and RT in locally advanced rectal cancer is relevant to this proposal. Patients with stage II-III rectal cancer received standard neoadjuvant chemoRT with capecitabine (825 mg/m^2 BID) on days of RT (50.4 Gy/1.8Gy/fraction) with the addition of veliparib during the treatment at varying dose cohorts (NCT01589419). Surgery was undertaken 5-10 weeks after completion of therapy. Thirty-two patients received study treatment with 30 being available for analysis. Seventy-three percent of patients had histologic downstaging at the time of surgery, including 28% ypCR. The NAR score for patients treated in the full dose cohort was 12.8. There were two documented DLTs (diarrhea and skin toxicity), neither of which compromised therapy. Twenty-eight percent of patients experienced any grade 3 of 4 AE with diarrhea (9%) being the most common. There were no surgical complications attributed to the treatment. The recommended dose for this phase II study is 400 mg PO BID throughout chemoRT. Pharmacokinetic studies confirmed no benefit to dose escalation beyond this level and did not interfere with fluoropyrimidine therapy (Michael 2015).

2.3.3 RT + capecitabine + MK-3475 (pembrolizumab/Arm 3)

Increasing evidence has been mounting to suggest that the immune system plays a major role in controlling tumor progression in a variety of tumors including colorectal cancer (Maas 2011). The immune score, first described in colorectal cancer by Galon et al, was calculated based on the combined analysis of CD8+ plus CD45RO+cells in the center of the tumors and at the invasive margins, and was found to correlate with prognosis (Pages 2009, Galon 2006). Interestingly, patients with colorectal tumors that had greater numbers of infiltrating CD8 and granzyme B-expressing T-cells (activated T-cells) had better survival compared to those with tumors that had lower numbers of infiltrating CD8 cells. Chemotherapeutic agents and radiation can increase the immunogenic properties of tumor cells by enhancing MHC class I expression, thereby increasing their vulnerability to cytotoxic lymphocytes. Another frequent effect of DNA damage inflicted by radiotherapy or chemotherapy is the increase in the expression of death receptors, enabling lysis of the tumor cells by Fas/CD95 ligand and TRAIL-positive immune effectors (Devaud 2013). The immunological impact of neoadjuvant chemoradiation in patients with rectal cancer was recently evaluated by Shinto et al. Pre-treatment biopsy and post- chemoradiation resected specimens from 93 rectal cancer patients who underwent neoadjuvant chemoradiation and radical resection were immunostained for CD8 and FOXP3, and the densities of stromal (STL) and intraepithelial (IEL) immunopositive TILs were determined separately. CD8+ STL density doubled after chemoradiation therapy, whereas FOXP3+ STL counts remained stable. High post-chemoradiation CD8 + STL density was associated with better prognosis and a high pre-treatment CD8/FOXP3 IEL ratio was a predictor of favorable tumor regression (Shinto 2014).

Furthermore, strong PD-L1 expression was observed in 30% of colorectal patients and was found to correlate with infiltration by CD8 (+) lymphocytes which did not express PD-1 (Droeser 2013). Both radiation and 5-FU induce the expression of PD-L1 on tumor cells through IFNγ production by CD8(+) T cells leading to an immune-suppressive environment and promoting PD-L1-mediated T-cell apoptosis (Dovedi 2014, Zhang 2008). The concomitant administration of stereotactic radiotherapy and anti PD-1 antibodies in B16-OVA melanoma or 4T1-HA breast

carcinoma tumors resulted in the development of antigen-specific T cell– and B cell–mediated immune responses that translated to better tumor response compared to either modality alone (Sharabi 2015). Specifically, in colorectal cancer xenograft model concomitant but not sequential administration of fractionated radiotherapy in combination with αPD-1 or αPD-L1 antibodies generated efficacious CD8(+) T-cell responses leading to better tumor response and survival compared to either modality alone (Dovedi 2014). These results could explain the adaptive response by tumor cells that mediates resistance to fractionated radiotherapy by expressing PD-L1 and therefore blocking PD-1/PD-L1 represents a valid strategy to overcome the adaptive tumor resistance to radiotherapy. Accordingly, we hypothesized that the addition of anti-PD-1 to neoadjuvant chemoradiation in rectal cancer could increase the CD8 TILs leading to a better pathological response rate.

Therefore, we propose to further study total neoadjuvant therapy with systemic chemotherapy (FOLFOX x 8 cycles) followed by novel radiosensitization with a targeted inhibitor or immune modulating agent plus fluoropyrimidine in a randomized phase II study platform for stage II and III rectal cancer. Experimental arms will be compared directly to a control arm (Arm 1) and not to each other. Arm 2 will use veliparib, 400 mg PO BID throughout neoadjuvant chemoRT, with capecitabine (825 mg/m^2 PO BID on days of radiotherapy), while Arm 3 will use MK-3475 (pembrolizumab), 200 mg IV every 3 weeks beginning on day 1 of RT for 6 total doses with capecitabine, 825 mg/m^2 PO BID on days of radiotherapy, as part of this Total Neoadjuvant Therapy clinical trial platform.

3.0 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Clinical Coordinating Department (CCD).

Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

Capecitabine is required for all patients. Consideration of prescription and procurement of capecitabine should be planned prior to study enrollment.

Submission of tumor tissue (FFPE) and blood is required for all patients who agree to the optional biobanking portion of this study. Investigators should check with their site Pathology department regarding release of tissue before approaching patients about participation in the trial. (See details of FFPE tumor sample submissions in Section 10.0.)

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.

3.1.2 Age ≥ 18 years at diagnosis.

3.1.3 ECOG Performance Status of 0, 1, or 2 (see Appendix A).

3.1.4 Diagnosis of adenocarcinoma of the rectum with the major portion of the tumor intact.

Note: Prior to randomization, the investigator must specify and document each of the following:

- distance of the lowest tumor margin from the anal verge; *and*
- intent for sphincter sparing or non-sphincter sparing surgical resection according to the primary surgeon; *and*
- the majority of the untreated tumor must be < 12 cm from the anal verge or below the peritoneal reflection as determined by the treating surgeon.

3.1.5 The tumor must be clinically determined to be locally advanced Stage II or Stage III rectal cancer and must also meet **any ONE** of the following criteria:

- *distal location (as defined by measurement on MRI, ERUS/pelvic CT [with IV contrast] scan or palpable on digital rectal exam [DRE])*: $cT_{3-4} \leq 5$ cm from the anal verge, any N
- *bulky:* any cT_4 or evidence that the tumor is adjacent to (defined as within 3 mm of) the mesorectal fascia on MRI or ERUS/pelvic CT (with IV contrast) scan
- *high risk for metastatic disease* with 4 or more regional lymph nodes (cN_2). **Clinical Nodal** or "**cN**" status for eligibility includes the total number of nodes (N_2 = 4 or more) in the mesorectal and superior rectal stations measuring ≥ 1.0 cm in any axis on cross sectional or endoscopic imaging. Nodes must measure 1.0 cm or greater to be considered positive for this eligibility requirement.
- *not a candidate for sphincter-sparing surgical resection prior to neoadjuvant therapy* (as planned by the primary surgeon)

Note: Clinical stage of the primary tumor and nodes may be determined locally by rectal endoscopic ultrasound or pelvic MRI (**pelvic MRI is strongly preferred**; see Appendix G. CT scan with IV contrast is acceptable provided there is evidence of T_4 and/or N_2 disease.

3.1.6 Patients must have the ability to swallow and retain oral medication.

3.1.7 Adequate hematologic function within 28 days before randomization defined as follows:
- ANC must be ≥ 1200/mm^3;
- Platelet count must be ≥ 100,000/mm^3; and
- Hemoglobin must be ≥ 10 g/dL.

3.1.8 Adequate hepatic function within 28 days before randomization defined as follows:
- total bilirubin must be ≤ ULN (upper limit of normal) for the lab unless the patient has a bilirubin elevation > ULN to 1.5 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; *and*
- alkaline phosphatase must be ≤ 3 x ULN for the lab; *and*
- AST must be ≤ 3 x ULN for the lab.

Note: If ALT is performed instead of AST (per institution's standard practice), the ALT value must be ≤ 3 x ULN; if both were performed, the AST must also be ≤ 3 x ULN. If AST and/or ALT is ≥ ULN but ≤ 3 x ULN, serologic testing for Hepatitis B and C must be performed and results for viral infection must be negative.

3.1.9 Adequate renal function within 28 days before randomization defined as serum creatinine ≤ ULN for the lab **and** measured or calculated creatinine clearance > 60 mL/min (see Appendix for instructions regarding calculation of creatinine clearance).

3.1.10 Serum potassium, magnesium, and calcium levels within 28 days before randomization must be within normal limits (WNL) for the lab.

3.1.11 International normalized ratio of prothrombin time (INR) within 28 days before randomization must be ≤ ULN for the lab. Patients who are therapeutically treated with an agent such as warfarin may participate if they are on a stable dose and no underlying abnormality in coagulation parameters exists per medical history. (See Section 5.6.9 for coumarin-derivative drug/drug interactions).

3.1.12 Patients with acquired immunodeficiency syndrome (AIDS-related illnesses) or known human immunodeficiency virus (HIV) disease **must**:
- Have a CD4 count ≥ 200 cells/μL within 30 days before randomization,
- Be off all antiretroviral therapy (prophylaxis/treatment) more than 60 days before randomization, *and*
- Have no evidence of opportunistic infections.

3.1.13 Pregnancy test (urine or serum beta-HCG) done within 72 hours before randomization must be negative (for women of childbearing potential only). If urine pregnancy results are positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.2 Ineligibility Criteria

Patients with one or more of the following conditions are NOT eligible for this study.

3.2.1 Rectal cancer histology other than adenocarcinoma (i.e., sarcoma, lymphoma, squamous cell carcinoma, mucosal melanoma, etc.).

3.2.2 Definitive clinical or radiologic evidence of metastatic disease. Required imaging studies must have been performed within 28 days prior to randomization. **Note: Distant clinical staging** to exclude patients with overt metastatic disease is determined by:

- Chest: CT scan (preferred); chest x-ray PA and lateral (acceptable); or PET scan (acceptable)
- Abdomen: CT scan with IV contrast (preferred); or MRI (acceptable)
- Pelvis: MRI (preferred; see Appendix G); or CT scan with IV contrast (acceptable)

(It is recommended that the same imaging tests that are performed before randomization be used at follow-up time points. ***Note:*** CT scans of the abdomen and pelvis must be performed with IV contrast.)

3.2.3 History of prior invasive rectal malignancy, regardless of disease-free interval.

3.2.4 Cardiac disease that would preclude the use of any of the drugs included in the GI002 treatment regimen. This includes but is not limited to:

- Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling temporary pacemaker
- Ventricular tachycardia or supraventricular tachycardia that requires treatment with Class Ia antiarrhythmic drugs (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic drug (e.g., sotalol, amiodarone, dofetilide). Use of other antiarrhythmic drugs is permitted.
- Second- or third-degree atrioventricular (AV) block unless treated with a permanent pacemaker
- Complete left bundle branch block (LBBB)
- History of long QT Syndrome
- QTc $\geq$ 450ms.

3.2.5 Sensory or motor neuropathy $\geq$ grade 2.

3.2.6 History of, or any evidence of, active non-infectious pneumonitis.

3.2.7 Active inflammatory bowel disease (i.e., patients requiring current medical interventions or who are symptomatic) or have a history of abdominal surgery or other medical condition that may, in the opinion of the treating physician, interfere with gastrointestinal motility or absorption.

3.2.8 Active autoimmune disease that has required systemic treatment within the past 2 years (i.e., with use of 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.

3.2.9 History of active TB (Bacillus Tuberculosis).

3.2.10 Active or chronic infection requiring systemic therapy.

3.2.11 Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study therapy. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI.

3.2.12 Active seizure disorder uncontrolled by medication.

3.2.13 Any antineoplastic therapy for this cancer before randomization.

3.2.14 Synchronous colon cancer.

3.2.15 Other invasive malignancy within 5 years before randomization. Exceptions are colonic polyps, non-melanoma skin cancer or carcinoma-in-situ of the cervix.

3.2.16 Antineoplastic therapy (e.g., chemotherapy or targeted therapy) for other invasive malignancy within 5 years before randomization. (For the purposes of this study, hormonal therapy is not considered chemotherapy.)

3.2.17 Prior treatment with an investigational compound being tested in this study (e.g., PARP inhibitor, anti-PD-1, anti-PD-L1, or anti-PD-L2).

3.2.18 Receipt of live vaccination within 28 days before randomization. Seasonal flu vaccines that do not contain live virus are permitted.

3.2.19 Major surgery within 4 weeks before randomization.

3.2.20 Any therapeutic pelvic radiation.

3.2.21 Known homozygous DPD (dihydro pyrimidine dehydrogenase) deficiency.

3.2.22 Any of the following because this study involves agents that have known or potential genotoxic or mutagenic, and teratogenic effects:

- pregnant women
- nursing women who are unwilling to discontinue nursing
- men or women of childbearing potential who are unwilling to employ adequate contraception (e.g., hormonal or barrier method of birth control; abstinence) for the duration of study treatment and for 4 months after the last dose of study therapy. (See Section 6.6.3)

3.2.23 Co-morbid illnesses or other concurrent disease that, in the judgement of the clinician obtaining informed consent, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens or prevent required follow-up.

4.0 REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

Tests, exams and other studies required before randomization are listed on Table 1. Requirements following randomization are outlined on Table 2 and Table 3.

Table 1. Tests, exams, and other requirements prior to randomization

Required Assessments	**Before randomization** *(see footnote a)*	
Consent form signed by the patient	X	
Determination of availability for release of primary tumor tissue from the diagnostic block (see Section 3.0)	X	
History & physical exam**b**	X	Within 28 days
Assessment of concurrent medications**c**	X	
Performance status (Appendix A)	X	
Height & weight	X	
CEA	X	
CBC/differential/platelet count	X	
Total bilirubin/AST/Alkaline phosphatase**d**	X	
Serum chemistries: glucose, BUN, sodium, potassium, chloride, bicarbonate or carbon dioxide, calcium, serum creatinine, magnesium	X	
Triiodothyronine (T3) *or* free triiodothyronine (FT3), *and* free thyroxine (FT4), *and* thyroid stimulating hormone (TSH)	X	
INR	X	
Creatinine clearance (calculated or measured)**e**	X	
12 Lead ECG with QTc interval measurement	X	
Local disease staging**f**	X	
Distant disease staging**g**	X	
Pregnancy test – Urine or Serum beta HCG**h**	X	Within 72 hours
Submission of archived primary tumor tissue**i**	X	Within 60 days after study entry

a Informed consent must be obtained before performance of any screening assessments; however, results of screening tests or examinations performed as standard of care before obtaining informed consent but within the timeframes outlined in Table 1 may be used rather than repeating required tests.

b Complete history and physical by a physician or other healthcare professional.

c Include all prescribed and over-the-counter medications, supplements, herbal therapies.

d ALT may be substituted for AST if required by the institution's standard practice.

e Both serum creatinine and creatinine clearance must be performed within 28 days prior to randomization.

f For local staging: May be either rectal endoscopic ultrasound or pelvic MRI; pelvic MRI is strongly preferred (see Appendix G)and requires submission via TRIAD (see Section 8.3.2) CT scan with IV contrast is acceptable if there is evidence of T_4 and/or N_2 disease (see Section 3.1.5).

g For distant (metastatic) staging: It is recommended that the same imaging tests performed before randomization be used at follow-up time points (***see Section 3.2.2 for preferred and acceptable imaging tests***). MRI imaging requires submission through TRIAD (see Section 8.3.2 and Appendix G).

h For women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

i **For patients who agree to the optional biobanking portion of this study.** See Section 10.0; the NRG-GI002 Pathology and Correlative Science Instructions.

Table 2. **For Arm 1 and Arm 2 Patients Only:** Tests, exams, and other requirements during study therapy and through Year 3

Required assessments *(See footnote **a**)*	**After randomization but before initiation of mFOLFOX6**	**During mFOLFOX6**	**Within 3 days *before* starting chemoradiation** *(see footnote **b**)*	**Weekly during chemoradiation** *(unless otherwise indicated)*	**30 days (+/- 7 days) after the last dose of chemoradiation**	**Preoperative** *(At surgery or within 14 days before surgery)*	**From surgery through Year 3* from randomization**
History & physical exam**c**		X	X	X	X	X *(see footnote **c**)*	X *(every 6 months)*
Adverse event assessment**d**		X	X	X	X	X	
Assessment of concurrent medications**e**		X**e**	X	X	X		
CBC/differential/ platelet count		X	X	X	X**f**	X	
Total bilirubin/ AST/Alk phos**g**		X	X	***Every other week*** *beginning with Day 1 of chemoRT*	X	X	
Serum chemistries: glucose, BUN, creatinine, sodium, chloride, bicarbonate or carbon dioxide							
Potassium, magnesium, and calcium			X	X ***Arm 2 only***	X		
INR				X *(see footnote**h**)*			
CEA		X ***(cycle 4 only)***	X			X	X *(every 6 months)*

Table continued on next page

Table 2. **For Arm 1 and Arm 2 Patients Only**: Tests, exams, and other requirements during therapy and through Year 3 *(continued)*

Required assessments *(See footnote **a**)*	**After randomization but before initiation of mFOLFOX6**	**During mFOLFOX6**	**Within 3 days *before* starting chemoradiation** *(see footnote **b**)*	**Weekly during chemoradiation** *(unless otherwise indicated)*	**30 days (+/-7 days) after the last dose of chemoradiation but before surgery**	**Preoperative** *(At surgery or within 14 days before surgery)*	**From surgery through Year 3* from randomization**
Thyroid function tests: triiodothyronine (T3) *or* free triiodothyronine (FT3), *and* free thyroxine (FT4), *and* thyroid stimulating hormone (TSH)						X	
Pregnancy testing **i**					X ***Arms 1 and 2***		
Disease imaging **j**			X *local and distant disease*			X *local and distant disease***k**	X *distant disease only every 6 months*
12 Lead ECG with QTc interval measurement					X ***Arm 2 only***		
Tumor (FFPE)**l**	*(see Table 1)*					X *(at surgery)*	
Whole Blood	X	X *(Within 3 days of **Cycle 5 only**)*	X			X	X**l** *(At **6 months** post surgery)*

a History and physical, blood tests, x-rays, scans, and other testing may be performed more frequently at the discretion of the investigator.

b Chemoradiation (chemoRT): RT plus capecitabine (Arm 1); RT plus capecitabine plus veliparib (Arm 2); . *Note*: A minimum of 4 daily RT treatments are required in any given week.

Table continued on next page

Table 2. **For Arm 1 and Arm 2 Patients Only:** Tests, exams, and other requirements during therapy and through Year 3 *(continued)*

c Updated history and physical with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up evaluations. **A formal assessment documenting clinical response of the primary rectal tumor (via digital rectal exam and proctoscopic or sigmoidoscopic exam) must be included with the preoperative assessment but may be done immediately before surgery** (see Section 12.1.1).

d See Section 7.0 for instructions adverse events reporting requirements.

e Include all prescribed and over-the-counter medications, supplements, herbal therapies and verify study therapy compliance through the review of patient's diary (Appendix F) and number of study drug tablets returned.

f For patients treated with veliparib (Arm 2 only), if cytopenias are documented that aren't attributable to another etiology, patients should be re-evaluated at the pre-operative visit. If persistent at that time and the cytopenia isn't attributable to another etiology, a hematology consultation and bone marrow biopsy could be considered post-operatively.

g ALT may be substituted for AST if required by the institution's standard practice (all Arms).

h ***Only for patients receiving concomitant capecitabine and a coumarin-derivative anticoagulant.*** Monitor INR weekly and for an additional **4 weeks** after the patient's last capecitabine dose (see Section 5.6.9).

i For women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy testing is not required after completion of investigational product unless required by institutional standards.

j All imaging results performed during this study must be recorded in the data collection forms. It is recommended that the same imaging tests performed before randomization be used at all follow-up time points. For local imaging of tumor/nodes, pelvic MRI is strongly preferred. MRI imaging requires submission through TRIAD (see Sections 8.3.2 and 14.2, and Appendix G). Clear evidence of distant (metastatic) disease development must be reported as progressive disease if before surgery or recurrent disease if after surgery.

k Imaging performed between chemoRT and surgery must be completed **no earlier than 4 weeks *and* no later than 2 weeks before surgery** after completion of chemoRT. Clear evidence of distant (metastatic) disease development must be reported as progressive disease if before surgery or recurrent disease if after surgery.

l Submission of blood at the defined time points and tumor (FFPE) from the diagnostic biopsy and from surgically resected primary tumor (or residual scar in the setting of pCR) is ***required for patients who agree*** (submit FFPE within 60 days after surgery). Postoperatively, research blood collection should occur at the first imaging visit (6 months) (see Section 10.0, the NRG-GI002 Pathology and Correlative Science Instructions).

Note:** *Following documented disease progression/recurrence or diagnosis of an invasive second primary/secondary malignancy, tests, exams, and assessments* ***are not required. However, patients will continue to be followed for survival and available cancer specimens (FFPE) will be collected (see Section 10.0) from patients who agree to optional biobanking.

Table 3. **For Arm 3 Patients Only:** Tests, exams, and other requirements during study therapy and through Year 3

Required assessments *(See footnote **a**)*	**After randomization but before initiation of mFOLFOX6**	**Within 3 days before Day 1 of each cycle of mFOLFOX6 (*beginning with Cycle 2*)**	**Within 3 days *before* starting chemoradiation** *(see footnote **b**)*	**Weekly during chemoradiation** *(unless otherwise indicated)*	**30 days (+/- 7 days) after the last dose of chemoradiation**	**30 days (+/- 3 days) and 90 days (+/-7 days) after the last dose of MK3475 (pembrolizumab)**	**Preoperative** *(Must be after last dose of MK3475 (pembrolizumab) but at surgery or within 14 days before surgery)*	**From surgery through Year 3* from randomization**
History & physical exam**c**		X	X	X	X		X *(see footnote **c**)*	X *(every 6 months)*
Adverse event assessment**d**		X	X	X	X	X**d**	X**d**	
CBC/differential/ platelet count		X	X	X**e**	X		X	
Assessment of concurrent medications**f**		X	X	X	X	X		
Total bilirubin/ AST/Alk phos**g**								
Serum chemistries: glucose, BUN, creatinine, sodium, chloride, bicarbonate or carbon dioxide		X	X	*Beginning Day 1 of chemoRT (see footnote**e**)*	X		X	
Potassium, magnesium, and calcium			X		X			
INR				X**h** *(see footnote **h**)*				
CEA		X ***(cycle 4 only)***	X				X	X *(every 6 months)*

Table continued on next page

Table 3: **For Arm 3 Patients Only:** Tests, exams, and other requirements during therapy and through Year 3 *(continued)*

Required assessments *(See footnote **a**)*	**After randomization but before initiation of mFOLFOX6**	**Within 3 days before Day 1 of each cycle of mFOLFOX6 (*beginning with Cycle 2*)**	**Within 3 days *before* starting chemoradiation** *(see footnote **b**)*	**Weekly during chemoradiation** *(unless otherwise indicated)*	**30 days (+/-7 days) after the last dose of chemoradiation**	**30 days (+/- 3 days) after the last dose of MK3475 (pembrolizumab)**	**Preoperative** *(Must be after last dose of MK3475 (pembrolizumab) but at surgery or within 14 days before surgery)*	**From surgery through Year 3* from randomization**
Thyroid function tests: triiodothyronine (T3) *or* free triiodothyronine (FT3), *and* free thyroxine (FT4), *and* thyroid stimulating hormone (TSH)			X	X *Every **3 weeks** (before each dose of MK-3475 (pembrolizumab) (see footnote**e**)*			X	
Pregnancy testing**i**								
Disease imaging**j**			X *local and distant disease***j**				X *local and distant disease***k**	X *distant disease only every 6 months*
12 Lead ECG with QTc interval measurement								
Tumor (FFPE)**l**	*(see Table 1)*						X *(at surgery)*	
Whole Blood	X	X *(Within 3 days of **Cycle 5 only**)*	X				X	X**l** *(At **6 months** post surgery)*

a History and physical, blood tests, x-rays, scans, and other testing may be performed more frequently at the discretion of the investigator.

b Chemoradiation (chemo RT) plus capecitabine plus MK-3475 (pembrolizumab) (Arm 3). *Note*: A minimum of 4 daily RT treatments are required in any given week.

c Updated history and physical with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up evaluations. **A formal assessment documenting clinical response of the primary rectal tumor (via digital rectal exam and proctoscopic or sigmoidoscopic exam) must be included with the preoperative assessment but may be done immediately before surgery** (see Section 12.1.1).

d See Section 7.0 for instructions adverse events reporting requirements.

Note: Preoperative adverse event assessment:

- for patients completing MK-3475 (pembrolizumab) and going to surgery: the day before surgery.
- for patients completing MK-3475 (pembrolizumab) and NOT going to surgery: 30 days from last MK-3475 (pembrolizumab) dose.
- for patients discontinuing MK-3475 (pembrolizumab) early and going to surgery: 8 weeks from RT+capecitabine or 30 days from last MK-3475 (pembrolizumab) dose, whichever is the latest, but not later than the day before surgery.
- for patients discontinuing MK-3475 (pembrolizumab) early and NOT going to surgery:8 weeks from RT+capecitabine or 30 days from last MK-3475 (pembrolizumab), whichever is the latest.

All patients will have an adverse event assessment at 90 days after the last dose of MK3475 (pembrolizumab).

e Following completion of chemoRT, continue to obtain CBC, LFTs, chemistries, thyroid function and pregnancy testing within 3 days before each dose of MK-3475 (pembrolizumab).

f Include all prescribed and over-the-counter medications, supplements, herbal therapies and verify study therapy compliance through the review of patient's diary (Appendix F) and number of study drug tablets returned.

g ALT may be substituted for AST if required by the institution's standard practice (all Arms).

h ***Only for patients receiving concomitant capecitabine and a coumarin-derivative anticoagulant.*** Monitor INR weekly and for an additional **4 weeks** after the patient's last capecitabine dose (see Section 5.6.9).

i For women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy testing is not required after completion of investigational product unless required by institutional standards.

j All imaging results performed during this study must be recorded in the data collection forms. It is recommended that the same imaging tests performed before randomization be used at all follow-up time points. For local imaging of tumor/nodes, pelvic MRI is strongly preferred. MRI imaging requires submission through TRIAD (see Sections 8.3.2 and 14.2, and Appendix G). Clear evidence of distant (metastatic) disease development must be reported as progressive disease if before surgery or recurrent disease if after surgery.

k The imaging due prior to initiation of chemo/RT should be done 3-4 weeks after completion of mFOLFOX6 but must be done prior to initiation of chemo/RT. Imaging performed between chemoRT and surgery must be completed **no earlier than 4 weeks *and* no later than 2 weeks before surgery** after completion of chemoRT. Clear evidence of distant (metastatic) disease development must be reported as progressive disease if before surgery or recurrent disease if after surgery.

l Submission of blood at the defined time points and tumor (FFPE) from the diagnostic biopsy and from surgically resected primary tumor (or residual scar in the setting of pCR) is ***required for patients who agree*** (submit FFPE within 60 days after surgery). Postoperatively, research blood collection should occur at the first imaging visit (6 months) (see Section 10.0, the NRG-GI002 Pathology and Correlative Science Instructions).

Note:** *Following documented disease progression/recurrence or diagnosis of an invasive second primary/secondary malignancy, tests, exams, and assessments* ***are not required. However, patients will continue to be followed for survival and available cancer specimens (FFPE) will be collected (see Section 10.0) from patients who agree to optional biobanking.

5.0 TREATMENT REGIMENS

5.1 Treatment regimen for Arm 1 (mFOLFOX6 followed by RT + capecitabine)

- Study therapy should begin within 2 weeks following randomization.
- Central venous access is strongly recommended.
- ***Results of laboratory safety assessments are to be reviewed prior to administration of study therapy.***
- Administer mFOLFOX6 in the order listed.
- Patient treatment setting (inpatient/outpatient) is per institutional guidelines.
- If there are no treatment delays, each mFOLFOX6 cycle = 2 weeks.
- Consideration of prescription and procurement of capecitabine should be planned prior to study enrollment.
- Instruct the patient to swallow capecitabine tablets whole (i.e., do not crush or chew).
- It is recommended that if a scheduled dose of capecitabine is missed, the dose can be taken within 6 hours; however, if more than 6 hours have passed since the scheduled dosing time, treatment should resume with the next regularly scheduled dose. Capecitabine compliance must be documented via the pill diary provided (Appendix E) and pill count.

Table 4. Treatment regimen for Arm 1 (mFOLFOX6 followed by RT +capecitabine)

Drug	Dose	Administration	Dosing Interval	Planned Duration
Oxaliplatin	85 mg/m^2	IV diluted in separate infusion bags of 250 ml D5W, given concurrently through separate lines connected by Y-line tubing, over approximately 2 hours. Flush infusion line *(see footnote **a**)*	Day 1 every 2 weeks	8 cycles
Leucovorin	400 mg/m^2			
5-Fluorouracil (5-FU)	400 mg/m^2	IV bolus recommended over 2–4 minutes immediately following oxaliplatin/leucovorin infusion		
	2400 mg/m^2	IV continuous infusion over 46-48 hours (total dose)		
Begin Day 1 of RT (3-4 weeks following the last dose of mFOLFOX6) *See Section 5.5 for RT schema*				
Capecitabine	825 mg/m^2	By mouth *(see footnotes **b, c**)*	Twice daily (only on days that RT is given)	Throughout RT

a Oxaliplatin is not compatible with normal saline solution or with 5-FU. The infusion line must be thoroughly flushed with D5W after administration with oxaliplatin. If oxaliplatin **is held**, administer leucovorin over 2 hours (preferred); however, administration time per institutional practice is permitted. Levoleucovorin can be substituted for leucovorin throughout this protocol, per institutional practice or as needed for drug availability, at a dose of 200 mg/m^2 (see Appendix D).

b Capecitabine should be taken in the morning and evening within 30 minutes after a meal (breakfast and dinner) on days when radiation therapy (RT) is given. If RT is not given on a regularly scheduled day (e.g., due to a holiday), capecitabine should not be taken.

c Use of a patient pill diary (Appendix E) to record capecitabine compliance is required.

5.2 **Treatment regimen for Arm 2 (mFOLFOX6 followed by RT + capecitabine + veliparib)**

- Study therapy should begin within 2 weeks following randomization.
- Central venous access is strongly recommended.
- ***Results of laboratory safety assessments are to be reviewed prior to administration of study therapy.***
- Administer mFOLFOX6 in the order listed.
- Patient treatment setting (inpatient/outpatient) is per institutional guidelines.
- If there are no treatment delays, each mFOLFOX6 cycle = 2 weeks.
- Consideration of prescription and procurement of capecitabine should be planned prior to study enrollment.
- Instruct the patient to swallow capecitabine tablets and veliparib capsules whole (i.e., do not crush or chew).
- It is recommended that if a scheduled dose of capecitabine or veliparib is missed, the dose can be taken within 6 hours; however, if more than 6 hours have passed since the scheduled dosing time, treatment should resume with the next regularly scheduled dose. Capecitabine and veliparib compliance must be documented via the pill diary provided (Appendix E) and pill count.

Table 5. Treatment regimen for Arm 2 (mFOLFOX6 followed by RT + capecitabine + veliparib)

Drug	Dose	Administration	Dosing Interval	Planned Duration
Oxaliplatin	85 mg/m^2	IV diluted in separate infusion bags of 250 ml D5W, given concurrently through separate lines connected by Y-line tubing, over approximately 2 hours. Flush infusion line.*(see footnote **a**)*.	Day 1 every 2 weeks	8 cycles
Leucovorin	400 mg/m^2			
5-Fluorouracil (5-FU)	400 mg/m^2	IV bolus recommended over 2–4 minutes immediately following oxaliplatin/leucovorin infusion		
	2400 mg/m^2	IV continuous infusion over 46-48 hours (total dose)		
Begin Day 1 of RT (3-4 weeks following the last dose of mFOLFOX6) *See Section 5.5 for RT schema*				
Capecitabine	825 mg/m^2	By mouth *(see footnotes **b, c**)*	Twice daily (only on days that RT is given)	Throughout RT
Veliparib	400 mg	By mouth *(see footnotes **b, c**)*	Twice daily	Throughout RT

a Oxaliplatin is not compatible with normal saline solution or with 5-FU. The infusion line must be thoroughly flushed with D5W after administration with oxaliplatin. If oxaliplatin **is held**, administer leucovorin over 2 hours (preferred); however, administration time per institutional practice is permitted. Levoleucovorin can be substituted for leucovorin throughout this protocol, per institutional practice or as needed for drug availability, at a dose of 200 mg/m^2 (see Appendix D).

b Capecitabine and veliparib should be taken together in the morning and evening on days when radiation therapy (RT) is administered. If RT is not given on a regularly scheduled day (e.g., due to a holiday), capecitabine should not be taken; however, veliparib should continue as outlined. Capecitabine should be taken within 30 minutes after a meal (breakfast and dinner); veliparib can be taken with or without food.

c Use of a patient pill diary (Appendix E) to record capecitabine and veliparib compliance is required.

5.3 Treatment regimen for Arm 3 (mFOLFOX6 followed by RT + capecitabine + MK-3475 (pembrolizumab)

- Study therapy should begin within 2 weeks following randomization.
- Central venous access is strongly recommended.
- ***Results of laboratory safety assessments are to be reviewed prior to administration of study therapy.***
- Administer mFOLFOX6 in the order listed.
- Patient treatment setting (inpatient/outpatient) is per institutional guidelines.
- If there are no treatment delays, each mFOLFOX6 cycle = 2 weeks; each MK-3475 (pembrolizumab) cycle = 3 weeks.
- Consideration of prescription and procurement of capecitabine should be planned prior to study enrollment.
- Instruct the patient to swallow capecitabine tablets whole (i.e., do not crush or chew).
- It is recommended that if a scheduled dose of capecitabine is missed, the dose can be taken within 6 hours; however, if more than 6 hours have passed since the scheduled dosing time, treatment should resume with the next regularly scheduled dose. Capecitabine compliance must be documented via the pill diary provided (Appendix E) and pill count.

Table 6. Treatment regimen for Arm 3 (mFOLFOX6 followed by RT + capecitabine + MK-3475 (pembrolizumab)

Drug	Dose	Administration	Dosing Interval	Planned Duration
Oxaliplatin	85 mg/m^2	IV diluted in separate infusion bags of 250 ml D5W, given concurrently through separate lines connected by Y-line tubing, over approximately 2 hours. Flush infusion line. *(see footnote **a**)*	Day 1 every 2 weeks	8 cycles
Leucovorin	400 mg/m^2			
5-Fluorouracil (5-FU)	400 mg/m^2	IV bolus recommended over 2–4 minutes immediately following oxaliplatin/leucovorin infusion		
	2400 mg/m^2	IV continuous infusion over 46-48 hours (total dose)		
Begin Day 1 of RT (3-4 weeks following the last dose of mFOLFOX6) *See Section 5.5 for RT schema*				
Capecitabine	825 mg/m^2	By mouth *(see footnotes **b, c**)*	Twice daily (only on days that RT is given)	Through-out RT
MK-3475 (pembrolizumab) See Section 9.4.2)	200 mg	IV over 30 minutes; a window of -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 25-40 minutes). See Section 9.4.2 for instructions on the preparation and administration of the infusion solution.	Every 3 weeks beginning Day 1 of RT	6 cycles

a Oxaliplatin is not compatible with normal saline solution or with 5-FU. The infusion line must be thoroughly flushed with D5W after administration with oxaliplatin. If oxaliplatin **is held**, administer leucovorin over 2 hours (preferred); however, administration time per institutional practice is permitted. Levoleucovorin can be substituted for leucovorin throughout this protocol, per institutional practice or as needed for drug availability, at a dose of 200 mg/m^2 (see Appendix D).

b Capecitabine should be taken in the morning and evening within 30 minutes after a meal (breakfast and dinner) on days when radiation therapy (RT) is given. If RT is not given on a regularly scheduled day (e.g., due to a holiday), capecitabine should not be taken.

c Use of a patient pill diary (Appendix E) to record capecitabine compliance is required.

5.4 Dose determinations

5.4.1 Calculations of BSA and/or Drug Doses

- Recommended chemotherapy doses will be provided at the time of randomization.
- Recalculations of BSA and drug doses are required if the patient has a 10% or greater weight change (+/-) from baseline or from the last weight used to calculate BSA and drug doses. At the investigator's discretion, the BSA and drug doses may also be recalculated prior to each treatment.

5.4.2 Rounding Doses

Rounding of drug doses is optional. If the treating physician decides to round the dose(s), follow these guidelines. (These also apply to dose modifications.)

- ***Oxaliplatin*** (85 mg/m^2 IV)
  Doses should be rounded to the nearest 1 mg.
- ***5-Fluorouracil*** (400 mg/m^2 IV and 2400 mg/m^2 IV)
  Doses should be rounded to the nearest 50 mg.
- ***Leucovorin*** (400 mg/m^2 IV)
  Doses should be rounded to the nearest 25 mg.
- ***Capecitabine*** (825 mg/m^2 PO)
  Doses should be rounded down to the nearest 500 mg or 150 mg.
- ***Veliparib*** (400 mg PO)
  Fixed dose; rounding is not applicable
- ***MK-3475*** (pembrolizumab) (200 mg total dose)
  Fixed dose; rounding is not applicable.

5.5 Radiation therapy

This protocol allows, but does not require, the use of Intensity Modulated Radiation Therapy (IMRT). Institutions using IMRT must be credentialed for IMRT for the modality chosen for treatment as specified by IROC Houston (Section 8.3). IGRT credentialing is not required; however, a facility questionnaire must be completed. Credentialing requirements can be found in Section 8.3.

Radiation Therapy Schema:

The treatment is delivered in 2 phases, an initial phase to treating the entire PTV_4500 including the PTV_5040 volume to 45 Gy, followed by a boost phase, treating the PTV_5040 with an additional 5.4 Gy to a total of 50.4 Gy. The fraction size is 1.8 Gy for all phases.

Phase	Target	Dose (Gy)	Number of Fractions	Fraction Size	Rx Length	Rx Days
Initial	PTV_4500	45	25	1.8 Gy	5 weeks	Monday through Friday
Boost	PTV_5040	5.4	3		3 days	
Total		50.4	28			

5.5.1 Treatment technology

This protocol requires treatment with photons with minimum nominal energy specification of 6 MV. IMRT is allowed and can be used either with static gantry or arcs (VMAT). Tomotherapy delivery is allowed.

5.5.2 Immobilization and simulation

Immobilization

Proper immobilization is important for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices. A custom immobilization device (such as Alpha Cradle or Vac-Loc for supine patients and an Alpha Cradle with bowel displacement device for prone patients) is suggested to minimize set-up variability. Simulation may be done with the patient in the supine "arms up" position for patients with very thin body habitus or the prone "arms up" position for patients of moderate or large body habitus.

Simulation imaging

CT Simulation is required and the images must be acquired using a CT-simulator with a slice thickness $\leq$ 3 mm. Care should be taken to use the smallest possible FOV that contains the entire surface of the patient with a 512x512 image matrix. Oral CT contrast is strongly suggested. An anal marker at the verge is required. The CT simulation must be performed with the patient in the treatment position.

Typical CT scan limits are mid-femur inferiorly to include the L2 vertebral body superiorly. The CT scan needs to include the following structures in their entirety: Treatment volumes (PTVs), bladder, and femoral heads.

5.5.3 Definition of target volumes and margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

The volumes are to be defined by planning CT/MRI techniques as well as PET scans when clinically appropriate. While PET scans are not mandated as part of the protocol, for those patients who have PET scans available, the information may be used to aid in treatment planning. The inferior extent of palpable tumors should be determined by physical examination.

Examples of contoured patients (anorectal atlas) are available for review on the NRG Oncology website (https://www.nrgoncology.org/ciro-gastrointestinal; Anorectal Atlas Link). These examples are excellent resources for the contouring of normal structures as well as GTV, CTV and PTV design, and their use is strongly encouraged.

Standard Name	Description	Validation Required/Required when applicable/Optional
GTV_5040	GTV to receive 50.4 Gy	Required
PTV_5040	PTV to receive 50.4 Gy	Required
CTV_4500	CTV to receive 45 Gy	Required
PTV_4500	PTV to receive 45 Gy	Required

Detailed specification:

Gross tumor volume (GTV): This includes the primary tumor and any pelvic nodes felt involved grossly with metastatic disease. Assessment of the primary tumor and nodal disease may be made on the basis of endoscopy, CT, PET-CT, MRI, or transrectal ultrasonography. The entire rectal circumference at the level of the tumor should be included as GTV_5040.

Clinical target volume (CTV_4500): This includes the GTV and the following nodal groups: perirectal nodes; presacral nodes; internal iliac; and common iliac nodes below the L5-sacral junction.

Planning target volume 4500 (PTV_4500): This will provide a margin around the CTV_4500 to compensate for the inter- and intra-fraction uncertainty consequent to daily setup uncertainty and to potential internal organ motion. By definition, the PTV_4500 will consist of a symmetrical 7 mm expansion around the CTV_4500. In the event that a PTV_4500 extends outside of the skin surface, the clinician should manually trim the PTV_4500 contours to be 3 mm inside the outer skin (unless there is direct skin involvement).

The following are guidelines for generating the CTV_4500 and PTV_4500 and PTV_5040. The CTV_4500 can be formed from the following CTV sub-volumes:

- CTV_rectal = Rectal GTV +1.5 cm radially, +2.5 cm craniocaudally along the mucosal surface. The radial expansion can be shrunk to within the mesorectal fascia and off organs/sidewall if no clinical/radiographic evidence of an involved mesorectal fascia OR T4 disease.
- CTV_nodal = Nodal GTV + 1.5cm symmetrical expansion. The symmetric expansion can be shrunk to within the mesorectal fascia and off organs/sidewall if no clinical/radiographic evidence of an involved mesorectal fascia.
- CTV_vessels = Uninvolved iliac vessels + 1.0 cm. This expansion can be trimmed off pelvic sidewall/bowel.
- CTV_presacral = the entire sacral hollow from mid S1-S5 and 8 mm tissue anterior to the anterior border of the sacral bone.
- CTV_perirectal = The mesorectum and perirectal lymphatic CTV should be identified on cross-sectional imaging and is best seen on an MRI. If the fascia cannot be confidently visualized, it can be generated by utilizing anatomic landmarks:
  - Posterior Border: anterior border of the sacrum and gluteus maximus
  - Lateral Border: ileum, piriformis and obturator muscles

  - Anterior Border: should include the interface with the bladder, vagina, uterus or prostate
  - Inferior Border: the levators
- The PTV_4500 is generated by expanding all of the above structures by 0.7 cm symmetrically and unifying them into one 3-dimensional volume for planning purposes.
- The PTV_5040 is an expansion of the GTV_5040 by 3 cm and the presacrum, this volume should not extend beyond PTV_4500.

5.5.4 Definition of critical structures

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	Description	Validation Required/Required when applicable/Optional
Bladder	Bladder	Required
Femur_R	Right femur	Required
Femur_L	Left femur	Required
Bowel_Small	Small Bowel	Required

Notes from RTOG Anorectal Atlas for contouring of normal structures:

Small Bowel:

The small and large bowel are important structures to consider when planning treatment. To avoid unnecessary time spent contouring the entire abdominal contents, they only need to be contoured up to ~ 1 cm above the PTV. This, in turn, implies that absolute volume of bowel (in cc) is more important than relative volume (in %). Otherwise cases with good exclusion of small bowel from the pelvis (e.g., with a belly board) will be unfairly penalized.

Femoral Heads:

The femoral head and neck should be avoidance structures. Only the femoral heads, not the neck should be drawn.

5.5.5 *Dose prescription*

Target Standard Name	Dose (Gy)	Fraction Size (Gy)	# of fractions	Dose specification technique
PTV_4500	45	1.8	25	Covering 95% of PTV
PTV_5040	50.4	1.8	3	Covering 95% of PTV

5.5.7 Planning technique

A 3D conformal radiotherapy planning technique must be used. If not using IMRT, field edges and MLC blocking must be conformal to the PTVs. The dose distributions must include corrections for tissue density heterogeneities. Regardless of planning technique, the dose prescription criteria specified in the section on compliance criteria (Section 5.5.7) must be used.

5.5.8 Compliance criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Vx_{Gy} (cc), Vx_{Gy} (%), $Vx_{\%}$(cc), $Vx_{\%}$(%): Volume (cc or %) receiving Dose (Gy, or %)
Dv_{cc}(Gy), Dv_{cc}(%), $Dv_{\%}$(Gy), $Dv_{\%}$(%): Dose (Gy or %) to Volume (cc or % of total volume)
D_{min}(Gy) or D_{min}(%): Minimum dose is defined to a volume that is the total volume minus 0.03 cc
D0.03cc(Gy) or D0.03cc(%): Maximum dose is defined to a volume of 0.03 cc
D_{mean}(Gy) or D_{mean}(%): Mean dose in Gy or %

For Normalization purposes two treatment plans are generated, one for each phase of treatment (initial 45 Gy, and subsequent boost volume to 50.4 Gy), each plan normalized to a PTV covering isodose volume of 95% as described in the prescription section (Section 5.5.5), $V_{95\%}$= 100%. A combination (plan sum) is required to evaluate the dosimetric compliance criteria for critical structures.

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met.

5.5.9 Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter*	Per Protocol	Variation Acceptable
PTV_4500	$D_{95\%}$ (%)	≥95	≥90
PTV_5040	$D_{95\%}$ (%) $D_{10(\%)}$ (%)	≥95 ≤110	≥90 ≤120
*Note: Percentiles are normalized to prescription doses of 45 Gy and 50.4 Gy respectively.			

Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
Bowel_Small	D_{150cc}(Gy)	≤15	≤16.5
	D_{120cc}(Gy)	≤35	≤38.5
	D_{70cc}(Gy)	≤40	≤44
	D_{35cc}(Gy)	≤45	≤49.5
	D0.03cc(Gy)	≤50	≤55
Femur_L & Femur_R	$D_{50\%}$(Gy)	≤30	≤33
	$D_{40\%}$(Gy)	≤40	≤44
	$D_{5\%}$(Gy)	≤45	≤49.5
	D0.03cc(Gy)	≤50	≤55
Bladder	D_{mean}(Gy)	≤40	≤44
E-PTVs	D_{1cc}(Gy)	≤49.5	≤54.5

E-PTVs include any non-PTV tissues.

Note: Constraints related to bowel and bladder are recommendations. Constraints will be scored but any Unacceptable Deviations will not affect the overall plan score. However, all femoral head constraints and the D0.03cc (Gy) for the Bowel_Small will be scored an Unacceptable Deviation if parameters are not met and will be counted in overall plan score.

5.5.10 Patient specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines. For photon IMRT plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Typically, measured dose distributions will be compared to planned dose distribution using a Gamma criterion of 4% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

5.5.11 Daily Treatment Localization/IGRT

Daily IGRT localization is required for patients treated with IMRT. Either a daily orthogonal kV pair, or CBCT (or MVCT) is acceptable. The boost plan should be imaged with daily CBCT. Institutional guidelines should be followed for daily treatment localization and IGRT. For patients not treated with IMRT, patients should be imaged with an Orthogonal kV (2D) image pair or CBCT (or equivalent) prior to the first fraction, and weekly henceforth. IGRT credentialing is not required for this protocol.

Management of Radiation Dose to the Patient from IGRT

NRG Oncology is concerned about the estimated doses given from IGRT, and is committed to limiting the imaging dose when IGRT is used in any of its protocols. This can be accomplished by avoiding the use of this technology to make small changes in patient positioning that are within the stated PTV margins. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g. requiring frequent corrections that are larger than the PTV margins). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

5.6 General Concomitant Medication and Supportive Care Guidelines

All concurrent/concomitant medications received within 30 days before the first dose of study therapy and 30 and 90 days after the last dose of study therapy are to be recorded.

5.6.1 G-CSF

- Use of growth factor support as primary prophylaxis to prevent neutropenia is discouraged but not prohibited; however, **do not administer G-CSF within 24 hours of chemotherapy or at any time during the radiotherapy phase of treatment**. See Section 6.0 for dose modifications and delays.
- Choice of growth factor is at the investigator's discretion.
- If needed, pegfilgrastim and filgrastim are recommended; however, if required by institutional standards, GM-CSF may be administered as an alternative.
- Loratadine (10 mg) or similar agents are permitted if pegfilgrastim is used.

5.6.2 Management of anemia

Chemotherapy should not proceed with ≥ grade 3 anemia. Transfusion is acceptable for improving the hemoglobin value to allow therapy to continue without delay. The patient should be assessed to rule out other causes of anemia. *Use of erythropoiesis-stimulating agents is prohibited.*

5.6.3 Management of diarrhea

Diarrhea is a commonly occurring toxicity with the therapies included in GI002. With combination chemoradiation, it is anticipated that diarrhea is likely to occur. Without appropriate treatment, diarrhea can be prolonged, severe, and lead to dehydration and other complications. (See Appendix B for clinical management of diarrhea. For patients randomized to Arm 3, also see Section 6.6.2 for supportive care guidelines of diarrhea/colitis with potential immunologic etiology.)

Management of diarrhea for patients randomized to Arms 1 and 2; and for patients randomized to Arm 3 (if diarrhea is deemed to be related to FOLFOX or CRT):

- Inform patients that they will experience diarrhea while on study therapy and possibly for several weeks after study therapy has stopped.
- Patients **must** be instructed to:
  - have ready access to antidiarrheal agents (e.g., loperamide) starting on Day 1 of treatment.
  - start antidiarrheal therapy at the very first sign of loose or more frequent stools
  - continue prophylactic therapy as directed
  - promptly report diarrhea symptoms
  - record the baseline number of daily stools, the occurrence of loose stools, and any anti-diarrheal treatment along with the daily dose of study therapy using the GI002 study diary (Appendix E). This record should be reviewed with the patient at each treatment visit.
  - report constipation *before* taking any laxatives or stopping antidiarrheal medication.

Patients who have multiple loose bowel movements and any worsening of fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash, or eosinophilia should be promptly evaluated for changes in liver function. (See Appendix B for sample patient instructions for diarrhea management. For patients randomized to Arm 3, also see Section 6.6.2 for supportive care guidelines of diarrhea/colitis with potential immunologic etiology.)

Refer to the ASCO Recommended Guidelines for Treatment of Cancer Treatment-Induced Diarrhea for additional recommendations regarding diarrhea (Benson 2004).

Antidiarrheal medications

All patients must be instructed to begin taking loperamide at the earliest sign of poorly-formed or loose stools (≥ grade 1). Early intervention is important for patient safety. See Section 6.0 for dose modifications and delays.

Aggressive supportive care should be provided for patients with grade 4 ANC and ≥ grade 3 diarrhea until neutropenia and diarrhea resolve. See Appendix B for clinical management of diarrhea. Hospitalization for evaluation and management of grade 3 or grade 4 complicated diarrhea, as defined in Appendix B, is strongly recommended. For patients randomized to Arm 3, also see Section 6.6.2 for treatment management/supportive care guidelines of diarrhea/colitis with potential immunologic etiology.

Management of diarrhea for Arm 3 (if diarrhea is thought to be related to pembrolizumab):

- Patients should be carefully monitored for signs and symptoms of immune related enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
- For patients with severe enterocolitis (Grade 3), MK-3475 (pembrolizumab) will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
  - For patients with moderate enterocolitis (Grade 2), MK-3475 (pembrolizumab) should be withheld. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

- All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

For patients randomized to Arm 3, also see Section 6.6.2 for treatment management/supportive care guidelines of diarrhea/colitis with potential immunologic etiology.

5.6.4 Management of nausea or vomiting (Arm 2)

Grade 3 nausea and vomiting has been seen in early phase studies with veliparib and capecitabine. Therefore, to optimize dose intensity and maintain quality of life, early initiation or prophylactic management with scheduled anti-emetic therapy (5HT-3 antagonists, metoclopramide, prochlorperazine) and/or lorazepam should be considered when patients begin treatment with veliparib and capecitabine. In addition, management should include counseling regarding these toxicities and may include brief interruption of dosing or dose modification. Investigators should also rely on standard clinical practice and guidelines for nausea management.

Antiemetic Therapy (all Arms)

Antiemetic therapy should be administered according to National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) clinical practice guidelines.

5.6.5 Management of pharyngolaryngeal dysesthesias

Oxaliplatin may cause discomfort in the larynx or pharynx associated with the sensation of dyspnea, anxiety, and swallowing difficulty. Exposure to cold can exacerbate these symptoms.

- Refer to Table 9 for dose modification instructions.
- Do NOT use ice chips or other forms of oral cryotherapy to decrease stomatitis in conjunction with oxaliplatin.
- Anxiolytics may be used at the physician's discretion.

5.6.6 Management of anaphylaxis

Oxaliplatin may cause anaphylactic reactions. Management of such reactions is per institutional guidelines.

5.6.7 Management of injection site reactions

Injection site reactions, including redness, swelling, and pain, has been reported with oxaliplatin. Extravasation, in some cases including soft tissue necrosis has occurred. Management is per institutional guidelines.

5.6.8 Prohibited Therapies

The following types of treatment, in addition to any cancer therapy other than the therapy specified in this protocol, are prohibited:

- **Chemotherapy**
  Administration of chemotherapy other than the chemotherapy specified in this protocol is prohibited **prior to** resection of the primary rectal cancer (see Section 5.9).
- **Targeted therapy**
  Administration of targeted therapy for malignancy is prohibited **prior to** resection of the primary rectal cancer (see Section 5.9).
- **Radiation therapy**
  Administration of radiation therapy other than the radiation therapy specified in this protocol is prohibited. (Radiation protocol therapy is outlined in Section 5.5.)
- **Live vaccines**
  Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal flu vaccines that do not contain live virus are permitted.
- **Systemic glucocorticoids**
  Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from study treatment; however, patients should continue to be followed per protocol. *(See Section 3.2 for additional medications that are prohibited in this trial.)*

5.6.9 Drug/drug interactions

- **Coumarin:** Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within 1 month after stopping capecitabine. These events occurred in patients with and without liver metastases.

  It is required INR be monitored carefully (at least weekly) while the patient is receiving treatment with capecitabine and warfarin concurrently and for an additional 4 weeks following the patient's last capecitabine dose. Institutional standards for this drug combination should be followed closely. Subcutaneous heparin or fractionated heparin products are permitted.

- **Phenytoin:** Increased phenytoin levels have also been reported in patients taking capecitabine concurrently with phenytoin and, therefore, need to be monitored.

5.6.10 Participation in Other Trials

If a GI002 patient is considering participation in another clinical trial (including supportive therapy trials), contact the NRG Oncology Clinical Coordinating Department.

5.7 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression/recurrence
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, *or*
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.8 Surgery

Surgery must be performed within 8 to 12 weeks following the last dose of radiotherapy. For patients in Arm 3, surgery must be performed within this window. Do not reschedule missed MK-3475 (pembrolizumab) doses. All doses of MK-3475 (pembrolizumab) must be given prior to surgery.

5.9 Adjuvant Therapy

Per protocol, adjuvant therapy is not recommended but allowed at the investigator's discretion. Any antineoplastic treatment given **after** surgical resection of the primary rectal cancer but before documentation of rectal cancer recurrence, second primary cancer or secondary malignancy must be reported via the GI002 Follow-up Folder in Medidata Rave.

6.0 TREATMENT MODIFICATIONS/MANAGEMENT

6.1 General instructions

- The descriptions and grading scales found in the revised CTCAE v4.0 will be utilized for AE reporting until March 31, 2018. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of CTCAE version 5.0, which can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- Treatment schedule changes for non-medical reasons: When rescheduling study therapy for non-medical adjustments, refer to the memo "Scheduling Protocol Therapy during the Holidays." This memo provides information regarding treatment over holidays/vacations and other non-medical delays (e.g. physician or patient schedules). This memo is updated annually and is posted on the CTSU Web site under the specific protocol memoranda. Any treatment schedule changes for non-medical reasons must be documented in the patient treatment record. (See Section 6.6.2 for instructions specific to MK-3475/pembrolizumab treatment delays.)
- In the event of disease progression/recurrence or diagnosis of an invasive second primary cancer or secondary malignancy, study therapy will be discontinued; further therapy is at the investigator's discretion. However, patients will continue to be followed off treatment for survival, and available cancer specimens (FFPE) will be collected (see Table 20A).

6.2 Treatment management radiation therapy

Treatment interruptions of radiation therapy are discouraged but may be necessitated by acute complications. The reason for and duration of any such interruption must be documented. **A minimum of 4 daily radiation therapy treatments are required in any given week.** Any missed radiation treatments will be made up at the end of the treatment schedule such that the total number of delivered 1.8 Gy fractions remains 28. If the sum total of radiation interruptions exceeds 7 normally scheduled treatment days, for reasons other than toxicity, this would represent a minor protocol violation.

During the chemoradiotherapy phase of treatment, if chemotherapy is held, radiation therapy will continue. If radiation is held, capecitabine will also be held; however, treatment with veliparib (Arm 2) and pembrolizumab (Arm 3) will continue unless otherwise contraindicated. Radiation may be held for grade 3 dermatitis radiation, grade 4 neutropenia, or other radiation-associated toxicity > grade 3 by CTCAE at the discretion of the treating radiation oncologist. Radiation should be restarted subsequent to recovery at the discretion of the radiation oncologist consistent with standard practice.

6.3 Treatment management mFOLFOX6

Chemotherapy dose modifications for all GI002 patients are detailed in Tables 7, 8, and 9. Additionally, the following mFOLFOX6 dose modification instructions must be followed:

- All doses must be based on the AE requiring the greatest modification.
- Any chemotherapy doses that have been reduced may not be escalated.
- If ≥ grade 2 toxicity occurs ***during the 46-48 hour infusion of 5-FU***, discontinue the infusion and refer to Tables 7 and 8 for dose modifications for the next cycle of mFOLFOX6.
- The leucovorin dose remains 400 mg/m2 regardless of changes in the 5-FU and oxaliplatin doses. If 5-FU is held, leucovorin should also be held.
- If oxaliplatin is discontinued, treatment should continue with 5-FU and leucovorin.
- If treatment with mFOLFOX6 must be discontinued for reasons other than disease progression/recurrence or diagnosis of a second primary cancer or secondary malignancy and

the patient is able to comply with all other aspects of the trial, timing of additional study treatment (RT + radiosensitizer[s]) may continue as planned.

- In the event of disease progression/recurrence or diagnosis of an invasive second primary cancer or secondary malignancy during mFOLFOX6, study therapy will be discontinued; further therapy is at the investigator's discretion. However, patients will continue to be followed off treatment for survival, and available cancer specimens (FFPE) will be collected.

Table 7. mFOLFOX6 dose levels

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level -1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Oxaliplatin	85	65	50	Discontinue
Leucovorin*	400	400	400	Discontinue
5-FU bolus	400	320	270	Discontinue
5-FU infusion	2400	1920	1600	Discontinue
*Levoleucovorin at 200 mg/m^2 can be substituted for leucovorin per institutional practice or as needed for drug availability (see Appendix D).				

Table 8. Treatment management for mFOLFOX6 (See Table 9 for oxaliplatin-specific toxicities.)

Important table instructions: • Dose modifications for mFOLFOX6 are based on the dose level changes on Table 7. • Dose modifications must be based on AEs that occurred during the cycle (column 2) ***and*** AEs present on the scheduled Day 1 of Cycles 2-8 (column 3). Refer to other applicable instructions in. • Refer to Section 5.6.2 for management of anemia. • Modifications in dose levels apply to 5-fluorouracil and oxaliplatin unless otherwise indicated; leucovorin doses remain unchanged. • Dose modifications must be based on the AE requiring the greatest modification.		
CTCAE v4.0 (until 3/31/18) CTCAE v5.0 (beginning 4/1/18) Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **b**)
Neutrophil count decreased: Grade 2 (ANC 1000-1199/mm^3); Grade 3, 4	Maintain dose	*Consider use of growth factors to avoid delay with subsequent cycles.* *Hold until ≥ 1200/mm^3. If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	Maintain dose	*Hold until ≥ 75,000/mm^3.* *If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Grade 4	↓ one dose level	*Hold until ≥ 75,000/mm^3.* ↓ one dose level

Table continued on next page

Table 8. Treatment management for mFOLFOX6 *(continued)*

CTCAE v4.0 (until 3/31/18) CTCAE v5.0 (beginning 4/1/18) Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE ***(See footnote a)***	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE ***(See footnote b)***
GI: **Diarrhea** *(despite optimal antidiarrheal management)* Grade 2	Maintain dose	↓ only 5-FU one dose level
Grade 3	↓ only 5-FU one dose level	↓ only 5-FU one dose level
Grade 4	↓ 5-FU one dose level *and* ↓ oxaliplatin one dose level *or* discontinue	Discontinue
Mucositis oral Grade 2	Maintain dose	↓ only 5-FU one dose level
Grade 3	↓ only 5-FU one dose level	↓ 5-FU two dose levels and ↓ oxaliplatin one dose level
Grade 4	↓ 5-FU two dose levels and ↓ oxaliplatin one dose level	Discontinue
Vomiting *(despite optimal antiemetics)* Grade 2	Maintain dose *or* ↓ one dose level	Maintain dose *or* ↓ one dose level
Grades 3, 4	↓ one dose level *or* discontinue	Discontinue
Investigations (hepatic): **Bilirubin, AST, alk phos** Grade 2	Maintain dose *or* ↓ oxaliplatin one dose level	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1, then:* ↓ oxaliplatin one dose level
Grade 3	↓ 5-FU *and* oxaliplatin one dose level	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1, then:* ↓ 5-FU *and* oxaliplatin two dose levels *or* discontinue
Grade 4	Discontinue	Discontinue
Febrile neutropenia: Grade 3	Maintain dose *or* ↓ one dose level	Maintain dose *or* ↓ one dose level
Grade 4	↓ one dose level *or* discontinue	↓ one dose level *or* discontinue
Infection: Grade 2	Maintain dose *or* ↓ one dose level	Maintain dose *or* ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level *or* discontinue	↓ one dose level *or* discontinue

Table continued on next page

Table 8. Treatment management for mFOLFOX6 *(continued)*

Other clinically significant AEs:[c] Grade 2	Maintain dose *or* ↓ one dose level	Maintain dose *or* ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or discontinue	Discontinue

a Resolved means that all clinically significant AEs are ≤ grade 1 (except neutrophils, which must be ≥ 1200/mm^3 and bilirubin, which must be ≤ the baseline grade) on Day 1 of the next scheduled cycle (i.e., treatment can be given without delay).

b Hold and check weekly. ***With exception of neutrophils and bilirubin, resume treatment when toxicity is ≤ grade 1.*** If toxicity has not resolved after 4 weeks of delay, discontinue mFOLFOX6 (see Section 6.3 for instructions regarding further study treatment).

c Determination of "clinically significant" AEs is at the discretion of the investigator.

Table 9. Treatment management for oxaliplatin-specific toxicities

Nervous System Disorders[a]		
Paresthesias/Dysesthesias/ Neuropathy (Peripheral motor; Peripheral sensory)	**1-7 day duration**	**> 7 day duration[b]**
Grade 1	Maintain dose	Maintain dose
Grade 2	Maintain dose[b]	Decrease ***oxaliplatin*** one dose level[b]
Grade 3	**First episode**: Decrease ***oxaliplatin*** one dose level [b] **Second episode**: Discontinue ***oxaliplatin***	Discontinue ***oxaliplatin***
Respiratory, thoracic and mediastinal disorders[a]		
Laryngopharyngeal dysesthesia	**1-7 day duration** *(intermittent or continuous)*	**> 7 day duration** *(intermittent or continuous)*
Grade 1 Grade 2	Maintain dose and consider increasing duration of oxaliplatin infusion to 6 hours	Maintain dose and consider increasing duration of oxaliplatin infusion to 6 hours
Grade 3	At the investigator discretion, either discontinue oxaliplatin or increase duration of infusion to 6 hours	Discontinue oxaliplatin
Grade 4	Discontinue oxaliplatin	Discontinue oxaliplatin
Respiratory, thoracic and mediastinal disorders[a]		
Dyspnea ≥ grade 2 **Hypoxia** ≥ grade 2 **Pneumonitis/pulmonary infiltrates** ≥ grade 2 **Pulmonary fibrosis** ≥ grade 2 **Cough** ≥ grade 3	Hold **all therapy** until interstitial lung disease is ruled out. • If non-infectious interstitial lung disease is confirmed, oxaliplatin must be discontinued. • If non-infectious interstitial disease is ruled out and infection (if any) has resolved, patients with persistent Grade 2 dyspnea or hypoxia can resume treatment at the discretion of the investigator.	

a Use the current CTCAE version (v4.0 until 3/31/18 or v5.0 beginning 4/1/18) to assess neurologic and respiratory toxicity for adverse event reporting.

b ***Hold oxaliplatin for ≥ grade 2 neurotoxicity***. When ≤ grade 1, resume treatment with dose modifications. If > grade 1 toxicity persists after 4 weeks of delay, discontinue oxaliplatin. Continue 5-FU + LV while oxaliplatin is held.

6.4 Treatment management capecitabine (Arm 1)

Capecitabine dose modifications for GI002 patients randomized to Arm 1 are detailed in Tables 10 and 11.

Additionally, the following dose modification instructions must be followed:

- All dose modifications should be based on the adverse event requiring the greatest dose modification.
- If RT is not administered (holiday, weekend, RT related toxicity, etc.), capecitabine is held.
- If capecitabine is held or discontinued, RT continues per protocol unless otherwise contraindicated.
- Capecitabine doses that have been reduced may not be escalated.
- In the event of disease progression/recurrence or diagnosis of an invasive second primary cancer or secondary malignancy during treatment with capecitabine/RT, study therapy will be discontinued; further therapy is at the investigator's discretion. However, patients will continue to be followed off treatment for survival, and available cancer specimens (FFPE) will be collected (see Table 20A).

Table 10. Capecitabine dose levels

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level -1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Capecitabine	825 (BID) *on days when RT is given*	620 (BID) *on days when RT is given*	465 (BID) *on days when RT is given*	Discontinue

Table 11. Treatment management for capecitabine (Arm 1)

Important table instructions: • Dose modifications for capecitabine are based on the dose level changes on Table 10. • **Hold capecitabine until any AE requiring dose modification returns to ≤ grade 1** unless indicated otherwise in the treatment management sections/tables. If recovery to ≤ grade 1 (or to other level specified) has not occurred after 3 weeks of delay, study therapy must be discontinued.	
CTCAE v4.0 (until 3/31/18) CTCAE v5.0 (beginning 4/1/18) Adverse Event/Grade	Modifications for AEs that REQUIRED DELAY IN TREATMENT
Neutrophil count decreased: Grades 3, 4	*Hold until ≥ 1200/mm³.If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	*Hold until ≥ 75,000/mm³.* *If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Grade 4	*Hold until ≥ 75,000/mm³.* ↓ one dose level
GI: **Diarrhea** *(despite optimal antidiarrheal management)* Grade 2, 3	***Treatment must be held for grades 2 and 3 diarrhea to avoid severe complications.*** 1st occurrence – ↓ one dose level 2nd occurrence –↓ one dose level 3rd occurrence – Discontinue
Grade 4	Discontinue
Mucositis - oral Grade 2	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level
Grade 4	Discontinue
Vomiting *(despite optimal antiemetics)* Grade 2	↓ one dose level
Grades 3, 4	↓ one dose level or discontinue
Investigations (hepatic): **Bilirubin, AST, alk phos** Grade 2	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1;* ↓ one dose level
Grade 3, 4	Discontinue

Table continued on the next page.

Table 11. Treatment management for capecitabine (Arm 1) *(continued)*

CTCAE v4.0 (until 3/31/18) CTCAE v5.0 (beginning 4/1/18) Adverse Event/Grade	Modifications for AEs that REQUIRED DELAY IN TREATMENT
Febrile neutropenia: Grade 3	Hold until clinical resolution, then ↓ one dose level
Grade 4	Discontinue
Infection: Grade 2	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level
Grade 4	↓ one dose level or discontinue
Skin and subcutaneous tissue disorders: **Palmer-planter erythrodysesthesia syndrome** Grades 2, 3	1st occurrence – ↓ one dose level 2nd occurrence – ↓ one additional dose level 3rd occurrence – discontinue
Other clinically significant AEs:* Grade 3	↓ one dose level
Grade 4	Discontinue
* Determination of "clinically significant" AEs is at the discretion of the investigator.	

6.5 Treatment management capecitabine and veliparib (Arm 2)

Capecitabine and veliparib dose modifications for GI002 patients randomized to Arm 2 are detailed in Tables 12 and 13.

Additionally, the following dose modification instructions must be followed:

- All dose modifications should be based on the adverse event requiring the greatest dose modification.
- If RT is not administered (holiday, weekend, RT related toxicity, etc.), capecitabine is held; however, veliparib and RT continue per protocol unless otherwise contraindicated.
- If capecitabine and/or veliparib are held or discontinued, RT continues per protocol unless otherwise contraindicated.
- Capecitabine doses that have been reduced may not be escalated.
- Veliparib doses that have been reduced may not be escalated.
- In the event of disease progression/recurrence or diagnosis of a second primary cancer or secondary malignancy during treatment with capecitabine, veliparib and RT, study therapy will be discontinued; further treatment is at the investigator's discretion. However, patients will continue to be followed off treatment for survival, and available cancer specimens (FFPE) will be collected (see Table 20A).

Table 12. Capecitabine and veliparib dose levels

	Dose Level 0 *Starting Dose* (mg/m^2)	**Dose Level -1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Capecitabine	825 (BID) *on days when RT is given*	620 (BID) *on days when RT is given*	465 (BID) *on days when RT is given*	Discontinue
	Dose Level 0 *Starting Dose* (total dose)	**Dose Level -1 (total dose)**	**Dose Level -2 (total dose)**	**Dose Level -3**
Veliparib	400mg (BID) *7 days/week*	300mg (BID) *7 days/week*	200mg (BID *7 days/week*	Discontinue

Table 13. Treatment management for capecitabine and veliparib (Arm 2)

Important table instructions: • **Hold capecitabine and veliparib doses until any AE requiring dose modification returns to ≤ grade 1** unless indicated otherwise in the treatment management sections/tables. If recovery to ≤ grade 1 (or to other level specified) has not occurred after 3 weeks of delay, study therapy must be discontinued. • All modifications in dose levels **apply to both capecitabine and veliparib unless otherwise noted.**	
CTCAE v4.0 (until 3/31/18) CTCAE v5.0 (beginning 4/1/18) Adverse Event/Grade	Modifications for AEs that REQUIRED DELAY IN TREATMENT
Neutrophil count decreased: Grades 2 (1000-1199/mm^3), 3, and 4	*Hold until ≥ 1200/mm^3.If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	*Hold until ≥ 75,000/mm^3.* *If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Grade 4	*Hold until ≥ 75,000/mm^3.* ↓ one dose level
GI : **Diarrhea** *(despite optimal antidiarrheal management)* Grade 2, 3	***Treatment must be held for grades 2 and 3 diarrhea to avoid severe complications.*** 1st occurrence – ↓ one dose level 2nd occurrence –↓ one dose level 3rd occurrence – Discontinue
Grade 4	Discontinue
Mucositis - oral Grade 2	Maintain dose or ↓ capecitabine one dose level
Grade 3	↓ capecitabine one dose level
Grade 4	Discontinue capecitabine
Vomiting *(despite antiemetics)* Grade 2	Hold and delay until ≤ grade 1, then ↓ one dose level
Grades 3, 4	↓ one dose level or discontinue chemotherapy
Investigations (hepatic): **Bilirubin, AST, alk phos** Grade 2	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1; then ↓* **one dose level**
Grade 3, 4	Discontinue chemotherapy

Table continued on the next page.

Table 13. Treatment management for capecitabine and veliparib (Arm 2) *(continued)*

CTCAE v4.0 (until 3/31/18) CTCAE v5.0 (beginning 4/1/18) Adverse Event/Grade	Modifications for AEs that REQUIRED DELAY IN TREATMENT
Febrile neutropenia: Grade 3	Hold until clinical resolution, then ↓ one dose level
Grade 4	Discontinue chemotherapy
Infection: Grade 2	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level
Grade 4	↓ one dose level or discontinue
Nervous system disorders: **Seizure** Grades 1, 2, 3, 4	Any event of seizure, regardless of grade or attribution, requires discontinuation of veliparib and discussion with the Medical Oncology Chair or Medical Oncology Protocol Officer regarding the decision to resume treatment.
Skin and subcutaneous tissue disorders: **Palmer-planter erythrodysesthesia syndrome** Grades 2, 3	1st occurrence – ↓ capecitabine one dose level 2nd occurrence – ↓ capecitabine one additional dose level 3rd occurrence – discontinue capecitabine
Other clinically significant AEs:* Grade 2	Maintain dose or ↓ attributable agent one dose level
Grade 3	↓ attributable agent one dose level
Grade 4	Discontinue attributable agent
* Determination of "clinically significant" AEs is at the discretion of the investigator.	

6.6 Treatment management capecitabine and MK-3475 (pembrolizumab) (Arm 3)

- Toxicities during chemoRT with capecitabine and MK-3475 (pembrolizumab) may be difficult to distinguish when first presenting. As a result, for any toxicity noted, please refer to both Table 15 (capecitabine) AND Table 16 (MK-3475/pembrolizumab) to determine if the AE and grade require one or more agent modification. Table instructions for individual agents should be followed independent of one another; however, both tables must be referenced for any overlapping toxicities.
- If RT is not administered (holiday, weekend, RT related toxicity, etc.), capecitabine is held; however, pembrolizumab continues per protocol unless otherwise contraindicated.
- If capecitabine is held or discontinued for capecitabine related toxicities (see Table 15), pembrolizumab and RT continue per protocol unless otherwise contraindicated.
- If pembrolizumab is held or discontinued for pembrolizumab related toxicities (see Table 16), capecitabine and RT continue per protocol unless otherwise contraindicated. Missed or held pembrolizumab doses are not to be rescheduled.

For toxicity-related delays, continue with the next scheduled dose following acceptable resolution of the AE. ***Note:*** **Surgery must be performed within 8 to 12 weeks following the last dose of RT.** For patients in Arm 3, surgery must be performed within this window. . Do not reschedule missed MK-3475 (pembrolizumab) doses. All doses of MK-3475 (pembrolizumab) must be given prior to surgery.

6.6.1 Capecitabine dose modification

Capecitabine dose modifications for GI002 patients randomized to Arm 3 are detailed in Tables 14 and 5 (capecitabine). See Section 6.6.2 and Table 16 for treatment management for MK-3475 (pembrolizumab).

Additionally, the following dose modification instructions must be followed:

- The current CTCAE version (v4.0 until 3/31/18 or v5.0 beginning 4/1/18) must be used to grade the severity of AEs. Refer to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- All dose modifications should be based on the adverse event requiring the greatest dose modification.
- Capecitabine doses that have been reduced may not be escalated.
- In the event of disease progression/recurrence or diagnosis of an invasive second primary cancer or secondary malignancy during treatment with capecitabine/pembrolizumab/RT, study therapy will be discontinued; further therapy is at the investigator's discretion. However, patients will continue to be followed off treatment for survival, and available cancer specimens (FFPE) will be collected (see Table 20A).

Table 14. Capecitabine dose levels

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level -1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Capecitabine	825 (BID) *on days when RT is given*	620 (BID) *on days when RT is given*	465 (BID) *on days when RT is given*	Discontinue

Table 15. Treatment management for capecitabine (Arm 3)

Important table instructions: • Dose modifications must be based on the AE requiring the greatest modification. • **Hold capecitabine until any AE requiring dose modification returns to ≤ grade 1** unless indicated otherwise in the treatment management sections/tables. For capecitabine, if recovery to ≤ grade 1 (or to other level specified) has not occurred after 3 weeks of delay, capecitabine must be discontinued. • Refer to Section 6.6 and Table 16 for MK-3475 (pembrolizumab) instructions.	
CTCAE v4.0 (until 3/31/18) CTCAE v5.0 (beginning 4/1/18) Adverse Event/Grade	Modifications for AEs that REQUIRED DELAY IN TREATMENT
Neutrophil count decreased: Grades 2 (1000-1199/mm^3), 3, and 4	*Hold capecitabine until ≥ 1200/mm^3.If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	*Hold until ≥ 75,000/mm^3.* *If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Grade 4	*Hold until ≥ 75,000/mm^3.* ↓ one dose level
GI: **Diarrhea** *(despite optimal antidiarrheal management)* Grade 2, 3	***Treatment must be held for grades 2 and 3 diarrhea to avoid severe complications.*** 1st occurrence – ↓ one dose level 2nd occurrence –↓ one dose level 3rd occurrence – Discontinue
Grade 4	Discontinue
Mucositis - oral Grade 2	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level
Grade 4	Discontinue
Vomiting *(despite optimal antiemetics)* Grade 2	↓ one dose level
Grades 3, 4	↓ one dose level or discontinue
Investigations (hepatic): **Bilirubin, AST, alk phos** Grade 2	*Hold until bilirubin returns to the **baseline grade** and AST and alk phos have returned to ≤grade 1;* ↓ one dose level
Grade 3, 4	Discontinue

Table continued on the next page.

Table 15. Treatment management for capecitabine (Arm 3) *(continued)*

CTCAE v4.0 (until 3/31/18) CTCAE v5.0 (beginning 4/1/18) Adverse Event/Grade	Modifications for AEs that REQUIRED DELAY IN TREATMENT
Febrile neutropenia: Grade 3	Hold until clinical resolution, then ↓ one dose level
Grade 4	Discontinue
Infection: Grade 2	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level
Grade 4	↓ one dose level or discontinue
Skin and subcutaneous tissue disorders: **Palmer-planter erythrodysesthesia syndrome** Grades 2, 3	1st occurrence – ↓ one dose level 2nd occurrence – ↓ one additional dose level 3rd occurrence – discontinue
Other clinically significant AEs:* Grade 3	↓ one dose level
Grade 4	Discontinue
* Determination of "clinically significant" AEs is at the discretion of the investigator.	

6.6.2 Treatment Management/Supportive Care Guidelines: MK-3475 (pembrolizumab) (Arm 3)

Adverse events (both non-serious and serious) associated with MK-3475 (pembrolizumab) exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. MK-3475 (pembrolizumab) must be withheld for drug-related toxicities and severe or life-threatening AEs.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record. ***Note:*** **Surgery must be performed within 8-12 weeks following the last dose of RT. If the dose interruption(s) would result in a delay of surgery, do not reschedule missed dose(s).**

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are also outlined in Table 16. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to MK-3475 (pembrolizumab).

Note: If after evaluation, the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

Table 16. Treatment Management and Supportive Care Guidelines for Related Adverse Events for MK-3475 (pembrolizumab)

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus)
	Recurrent Grade 3 or Grade 4	Permanently discontinue		• Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion

Table continued on next page.

AST or ALT elevation or Increased Bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders

Table continued on next page.

Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1–2mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade3 or Grade4	Permanently discontinue		

[a] AST/ALT: >3.0-5.0 x ULN if baseline normal; >3.0-5.0 x baseline, if baseline abnormal; bilirubin:>1.5-3.0 x ULN if baseline normal; >1.5-3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0-20.0 x baseline, if baseline abnormal; bilirubin:>3.0-10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin:>10.0xULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

6.6.3 *Other Considerations*

Diet

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

Contraception and Pregnancy

Study therapy may have adverse effects on a fetus in utero. Furthermore, it is not known if the study drugs have transient adverse effects on the composition of sperm.

For this trial, male patients will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female patients will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 90 days (Arms 1 and 20 and 120 days (Arm 3) after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):
- intrauterine device (IUD)
- vasectomy of a female patient's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):
- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 90 days (Arm 1 and Arm 2) or 120 days (Arm 3) after the last dose of trial therapy. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

Use in Pregnancy (Arm 3)

If a patient inadvertently becomes pregnant while on MK-3475 (pembrolizumab), the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the NCI and to Merck without delay and within 24 hours to the NCI and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the NCI. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the NCI and to Merck and followed as described above and in Section 7.4.7.

Use in Nursing Women (Arm 3)

It is unknown whether MK-3475 (pembrolizumab) is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

7.0 ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Study Agents

7.1.1 Investigational agents

The investigational agents in NRG-GI002 are ***veliparib*** (NSC #737664)/ARM 2 and ***MK-3475 (pembrolizumab)(***NSC #776864***)/*****ARM 3**, which are being made available under INDs sponsored by the DCTD, NCI.

7.1.2 Commercial agents

The commercial agents in NRG-GI002 are 5-fluorouracil (NSC #19893), leucovorin (NSC #3590), oxaliplatin (NSC #266046), and capecitabine (NSC #712807).

7.2 Adverse Events and Serious Adverse Events

7.2.1 Adverse Event Characteristics

CTCAE term (Adverse event [AE] description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting until March 31, 2018. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.2.2 Definition of an adverse event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH] E2A, E6).

Adverse event reporting encompasses all aspects of the protocol including radiation therapy, surgery, and drug.

7.2.3 Definition of a serious adverse event

Any adverse event (experience) occurring at any dose that results in **ANY** of the following outcomes:

- Death
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours)
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

7.3 Adverse Events for the Study Agents

7.3.1 Commercial agents

Refer to the current FDA-approved package insert for detailed pharmacologic and safety information.

FOLFOX (5-florouracil, leucovorin, and oxaliplatin):

Common adverse events (> 20%) include: alopecia, mucositis, anemia, diarrhea, nausea, vomiting, infection, palmar-plantar erythrodysesthesia, peripheral motor and sensory neuropathies

Less common events (≤ 20%) include: photophobia, blurred vision, eyelid function disorder, hearing impaired, and high blood pressure

Rare but serious events (< 3%) include: treatment related secondary malignancy and Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Capecitabine:

Common adverse events (> 20%) include: edema, palmar-plantar erythrodysesthesia anemia, infection, thrombocytopenia, fatigue, and diarrhea.

Less common events (≤ 20%) include: blurred vision, restlessness, and ataxia.

Rare but serious events (< 3%) include: hypersensitivity reaction, and myocardial infarction/ischemia.

7.3.2 Investigational agent veliparib (ABT-888)

For veliparib, expectedness of adverse events is based on the current NCI Specific Protocol Exceptions to Expedited Reporting (SPEER) for veliparib.

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2310 patients.* Below is the CAEPR for veliparib (ABT-888).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Table 17. Comprehensive Adverse Events and Potential Risks list (CAEPR) for ABT-888 (veliparib) NSC 737664)

Version 2.4, May 13, 2018[1]

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
		Treatment related secondary malignancy	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Seizure	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
VASCULAR DISORDERS			
		Thromboembolic event[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Thromboembolic events, including deep vein thrombosis and pulmonary embolism, have been observed at a higher frequency compared to control arm when administered in combination with temozolomide.

Adverse events reported on ABT-888 (Veliparib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ABT-888 (Veliparib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Cardiac disorders - Other (Takotsubo cardiomyopathy); Heart failure; Left ventricular systolic dysfunction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Colonic obstruction; Dental caries; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Lower gastrointestinal hemorrhage; Mucositis oral; Obstruction gastric; Rectal hemorrhage; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Flu like symptoms; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (cirrhosis)
INFECTIONS AND INFESTATIONS - Appendicitis; Catheter related infection; Infections and infestations - Other (peritonsillar abscess); Lung infection; Lymph gland infection; Mucosal infection; Sepsis; Shingles; Skin infection; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Radiation recall reaction (dermatologic)
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Lipase increased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia

7.3.3 Investigational agent MK-3475 (pembrolizumab)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab), NSC 776864).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Table 18. Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab) NSC 776864) **Version 2.5, December 27, 2019[1]**

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
	Lymph node pain[2]		
	Thrombotic thrombocytopenic purpura[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypohysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		*Arthralgia[2] (Gr 2)*
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.3.4 Radiation therapy adverse events

- Short Term

  Fatigue, loss of appetite, and nausea are anticipated systemic reactions to radiation treatment. Skin erythema, desquamation, and diarrhea are potential local reactions.
- Long Term

  Long term effects include bowel obstructions; bowel dysfunction presented as fecal incontinence to gas, loose stools, evacuation problems or urgency; and sexual dysfunction.

7.4 Expedited Reporting of Adverse Events

- All serious adverse events that meet expedited reporting criteria defined in Table 19 will be reported via the CTEP Adverse Event Reporting System (CTEP-AERS), accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers. The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). The reporting timelines are outlined in Table 19.
- For expedited reporting purposes only: AEs for the agent that are bold and italicized in the CAEPR (i.e., those listed in the SPEER column [Sections 7.3.2 and 7.3.3]) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
- Submitting a report via CTEP-AERS serves as notification to the NRG Statistics and Data Management Center (SDMC) and satisfies NRG requirements for expedited adverse event reporting.
- In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to **CTEP by telephone at 301-897-7497 and to** NRG Oncology by phone at 412-339-5300. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.1 Expedited reporting methods

- **CTEP-AERS 24-hour Notification:** Per CTEP NCI Guidelines for Adverse Events Reporting, a **CTEP-AERS 24-hour notification** must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS **5 Calendar Day Report** (see Table 19).
- **CTEP-AERS 10 Calendar Day Report** requires that a complete report is electronically submitted **within 10 calendar days** of learning of the AE (see Table 19).
- **Supporting source documentation** is requested by the IND sponsor (CTEP/DCTD) for this study as needed to complete adverse event review. All CTEP-AERS documentation is faxed to CTEP at 301-897-7404. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page.

7.4.2 Expedited reporting requirements (CTEP-AERS-24, CTEP-AERS)

Expedited reporting requirements begin with the administration of the first study therapy dose. Expedited reporting requirements for all patients are provided in Table 19.

Table 19. Expedited reporting requirements for adverse events that occur on studies under an IND[1]
Expedited reporting requirements for adverse events that occur on studies under an IND include: within 30 days of the last administration of the investigational agent (veliparib or MK-3475 [pembrolizumab]) and/or commercial agents (5-fluorouracil, leucovorin, oxaliplatin, and capecitabine), within 90 days of the last administration of the investigational agent MK-3475 (pembrolizumab), or within 30 days of initiation of another anti-cancer therapy (whichever occurs first.)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect
6) Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour, 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR for veliparib.

Expedited AE reporting timelines are defined as:

"24-Hour, 5 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

"10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent and 90 days after the last administration of MK-3475 (pembrolizumab) and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report with 5 calendar days for:

All Grade 4 and Grade 5 AEs

Expedited 10 calendar days reports for:

Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

Grade 3 adverse events

Effective Date: May 5, 2011

7.4.3 Additional protocol-specific requirements or exceptions to expedited reporting

- **Protocol-specific expedited reporting requirements:** For this study, the following secondary malignancies require expedited reporting via CTEP-AERS from the first dose of study therapy until the end of the patient's follow-up:
  - Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- **Protocol-specific expedited reporting exceptions:** For this study, the following adverse events, including hospitalizations for these events, do **not** require expedited reporting via CTEP-AERS:
  - *Investigations:* Grade 4 decreased neutrophil count, platelet count, and white blood cell count.
  - *Neoplasms-malignant* (i.e., a second primary cancer) determined by the investigator to NOT be most probably related or definitely related to treatment for malignancy.
  - AEs following a documented invasive rectal cancer recurrence or tumor progression.

7.4.4 ***Protocol-specific exceptions to expedited reporting of serious adverse events for the investigational agents (veliparib and MK-3475 (pembrolizumab) are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the ABT-888 (veliparib) CAEPR and the MK-3475 (pembrolizumab) CAEPR.*** Reporting to the Site IRB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) responsible for oversight of the patient according to institutional policy.

7.4.5 Secondary malignancy

A ***secondary*** malignancy is a cancer that is caused by a treatment for previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur on NCI-sponsored trials either during or following treatment must be reported via CTEP-AERS within 10 days of learning of the secondary malignancy. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the GI002 Follow-up Folder in Medidata Rave. Supporting documentation should be uploaded into the relevant form in the Follow-up folder in Medidata Rave using available upload fields within those forms. Please upload each document into a different upload field, as any later uploads into a given field erases the document that exists there.

7.4.6 Second malignancy

A ***second*** malignancy is a cancer that is unrelated to the treatment of a prior malignancy and is **NOT** a metastasis from the initial malignancy. Second malignancies require **ONLY** routine reporting within the GI002 Follow-up folder in Medidata Rave (see Section 7.6).

7.4.7 Expedited reporting of pregnancy, fetal death/pregnancy loss, and death neonatal

Any pregnancy, fetal death/pregnancy loss, or death neonatal occurring in a female patient or partner of a male patient from the time of consent to 90 days (Arms 1 and 2) or to 120 days (Arm

3) following the last dose of study therapy, must be reported via CTEP-AERS as a medically significant event. Definitions and reporting instruction for these events are provided in the Cancer Therapy Evaluation Program's (CTEP) revised NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6) located at the following CTEP website: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf). Upon learning of a pregnancy, fetal death/pregnancy loss, or death neonatal that occurs during study or within 3 months following the last dose of study therapy the investigator is **required** to:

- Immediately discontinue study therapy.
- Call the NRG Oncology Clinical Coordinating Department (CCD).
- Within 5 working days of learning of the event, and as required by the NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6):
  - Create and submit a CTEP-AERS report;
  - Complete the Pregnancy Information Form (located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) and fax the form to CTEP at 301-897-7404.
- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Information Form used for the initial report.
- Pregnancy loss is defined in CTCAE as "Death in utero." Beginning April 1, 2018, report pregnancy loss expeditiously as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss is not reported as a Grade 5 event.

7.5 Routine Reporting of Adverse Events

7.5.1 Reporting routine adverse events through Medidata Rave

- Reporting of routine adverse events is done through Medidata Rave (see Section 14.0).
- **All ≥ grade 2 adverse events** that occurred during study therapy must be reported on the GI002 Adverse Event and Treatment forms through Medidata Rave, regardless of whether these adverse events are expected or unexpected.
- Supporting documentation for each AE reported on the GI002 Adverse Event forms through Medidata Rave must be maintained in the patient's research record.

7.5.2 Schedule for reporting routine adverse events

Adverse events are to be submitted through Medidata Rave, **even if no AEs were experienced by the patient**. Submit the GI002 Adverse Event and Treatment forms according to the following schedule:

- *During mFOLFOX6:* at the end of each cycle and 3 to 4 weeks after the last cycle but before starting chemoRT;
- *During chemoRT:* weekly and 30 days (+/- 3 days) after the last dose of chemoRT;
- *Before surgery:* ***For Arms 1 and 2****:* within 14 days before surgery. If surgery is not performed, AE assessment should be submitted 8-12 weeks after the last dose of chemoRT. ***For Arm 3*****:** If patient completed 6 total doses of MK3475 (pembrolizumab): report AEs the day before surgery. If surgery is not performed, AE assessment should be submitted 30 days from last dose of MK3475 (pembrolizumab). If patient discontinues MK3475 (pembrolizumab) early and if surgery is performed, report AEs 8 weeks from RT and capecitabine or 30 days from last MK3475 (pembrolizumab), whichever is the latest, but not later than the day before surgery. If patient discontinues MK3475 (pembrolizumab) early and if surgery is not performed, report AEs 8 weeks from RT and capecitabine or 30 days from last MK3475 (pembrolizumab), whichever is the latest.

7.6 Reporting Rectal Cancer Progression/Recurrence and Second Primary Cancer

Report rectal cancer progression/recurrence and second primary cancer (a malignancy that is unrelated to the treatment of a prior malignancy and which is not a metastasis from the initial malignancy) within the GI002 Follow-up folder in Medidata Rave. Supporting documentation should be uploaded into the relevant form in the Follow-up folder in Medidata Rave using available upload fields within those forms. Please upload each document into a different upload field, as any later uploads into a given field erases the document that exists there. (See Section 7.4.5 for reporting instructions for ***secondary*** malignancies.)

8.0 REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

8.1 Cancer Therapy Evaluation Program registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

8.2 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI (CTSU).

8.2.1 IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Protocol Specific Requirements for NRG-GI002 Site Registration

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. A primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link on the CTSU website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory Support System (RSS) to comply the protocol specific requirement. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

8.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select NRG, and protocol number NRG-GI002;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.).

8.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

8.2.4 Checking Your Site's Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on *Regulatory* at the top of your screen;
- Click on Site Registration;
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status given only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

8.3 RT Credentialing Requirements

For detailed information on the specific technology requirement required for this trial, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Credentialing is not required for 3DCRT. For IMRT, IROC Houston will notify the institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

RT Credentialing Requirements	Web Link for Procedures and Instructions: **http://irochouston.mdanderson.org**		
	Treatment Modality		Key Information
	3DRT	IMRT	
Facility Questionnaire	No credentialing required	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	No credentialing required	X	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston mdanderson.org)
Phantom Irradiation	No credentialing required	X	An IMRT H&N phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston mdanderson.org). Tomotherapy, Cyberknife and other unique treatment delivery modalities must be credentialed individually.

8.3.1 Digital RT Data Submission to NRG Oncology Using TRIAD

TRIAD is the American College of Radiology (ACR) image exchange application used by the NRG Oncology. TRIAD provides sites participating in NRG clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

8.3.2 TRIAD Access Requirements

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

Site staff that will be submitting images via TRIAD will need to register with CTEP and have a valid and active CTEP-IAM account.

- Must be registered as an Associate, Associate Plus, Non-Physician Investigator, or Investigator registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in Registration and Credential Repository (RCR).
- To submit images, site staff must hold the TRIAD Site User role on an NCTN or ETCTN roster. Individuals requiring a TRIAD Site User role should contact the person holding a primary role at the site for their affiliated NCTN or ETCTN roster.
- All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installations:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.4 Patient Enrollment

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.4.1 Reimbursement

To receive site reimbursement for biospecimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the NRG-GI002 specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement for CTEP funding.

Further instructional information is provided on the OPEN tab of the CTSU Member side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.5 Study Withdrawal

8.5.1 Investigator-initiated discontinuation of study therapy

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study therapy if one of the following occurs:

- the patient develops a serious side effect that he or she cannot tolerate or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the study therapy or other treatments for rectal cancer becomes available.

If study therapy is stopped, study data and other materials should be submitted according to the study schedule unless the patient withdraws from the study (see Section 8.5.3).

8.5.2 Patient-initiated discontinuation of study therapy

Even after a patient agrees to take part in this study, he or she may stop study therapy or withdraw from the study at any time. If study therapy is stopped but the patient still allows the investigator to submit information, study data and other materials should be submitted according to the study schedule.

8.5.3 Patient-initiated withdrawal from the study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow-up data to be submitted to NRG Oncology SDMC), the investigator must provide NRG Oncology SDMC with written documentation of the patient’s decision to fully withdraw from the study.

9.0 DRUG INFORMATION

9.1 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by the responsible investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Patients must be enrolled and randomized to veliparib (Arm 2) *or* MK-3475 (pembrolizumab) (Arm 3) prior to submitting the agent request to PMB.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

9.1.1 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB Coordinator via email.

9.2 PMB policies and guidelines:

http://ctep.cancer.gov/branches/pmb/agent_management.htm

Refer to the Policy and Guidelines for Investigational Agent Ordering for order processing time and conditions. Normal order processing time is two business days. An express courier account number must be provided for next-day delivery.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx

- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9.3 Commercial Agents

The commercial study agents are 5-fluorouracil, leucovorin, oxaliplatin, and capecitabine.

9.3.1 Availability/Supply

5-fluorouracil (NSC #19893), leucovorin (NSC #3590), oxaliplatin (NSC #266046), and capecitabine (NSC #712807) will not be provided and must be obtained by the investigator from commercial supply. Please see Section 5.1 (Table 4), Section 5.2 (Table 5), and Section 5.3 (Table 6) for administration instructions. Refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for instructions for standard drug preparation, handling, and storage.

9.3.2 Adverse Events

For adverse events and potential risks associated with 5-fluorouracil, leucovorin, oxaliplatin, and capecitabine, please refer to Section 7.3.1, to the current FDA-approved package insert provided with each drug, and to the site-specific pharmacy.

9.4 CTEP IND Agents

The CTEP IND (investigational) agents are veliparib for patients randomized to Arm 2 and MK-3475 (pembrolizumab) for patients randomized to Arm 3. There are no investigational study agents in Arm 1.

9.4.1 Veliparib Capsule (NSC 737664)

Chemical Name: 1*H*-Benzimidazole-7-carboxamide, 2-[(2*R*)-2-methyl-2-pyrrolidinyl

Other Names*:* ABT-888, A-861695.0

Classification*:* Poly (ADP-ribosome) polymerase (PARP) Inhibitor

CAS Registry Number*:* 912444-00-9

Molecular Formula: $C_{13}H_{16}N_4O$ **M.W.:**244.29

Approximate Solubility*:* Veliparib is freely soluble at pH < 6.9, soluble at pH 6.9 to 7.1, and slightly soluble at pH > 7.1.

Mode of Action*:* Veliparib inhibits the formation of poly (ADP-ribose) (PAR) polymers in vitro and in vivo. It inhibits the repair of DNA when the DNA is damaged by cytotoxic agents. Veliparib increases antitumor efficacy when added to DNA-damaging therapies such as temozolomide, cisplatin, carboplatin, cyclophosphamide, irinotecan, or radiation therapy.

Description*:* White to light yellow solid.

How Supplied: AbbVie supplies and Division of Cancer Treatment and Diagnosis (DCTD) distributes veliparib. Veliparib capsules are available in 100 mg immediate release capsules. The

inactive ingredients are microcrystaline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. It may contain FD&C blue#1, FD&C yellow #6, or FD&C yellow #5. The capsules are packaged in HDPE bottles, and each HDPE bottle contains 64 capsules.

Veliparib capsules may be repackaged from the supplied HDPE bottles into amber (or other low-actinic) child resistant pharmacy dispensing bottles. Expiration will be 30 days from the repackaging date (or the original retest date, whichever is earlier) when stored at 15°C to 25°C (59°F to 77°F).

Storage: Store the original bottle at 15° to 25° C (59° to 77° F). If a storage temperature excursion is identified, promptly return veliparib to 15° and 25° C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf-life stability studies for veliparib capsules are on-going.

Route(s) of Administration: Oral

Method of Administration: Administer veliparib orally without regards to meals.

Potential Drug Interactions (DDIs): Nonclinical studies suggest ABT-888 is a substrate of P-gp, OCT2, and MATE1/MATE2K transporters. Co-administration of ABT-888 with strong inhibitors of P-gp, OCT2, and MATE1/MATE2K drugs may result in a decrease of ABT-888 renal clearance and an increase in ABT-888 plasma concentration. Therefore, use caution when administering ABT-888 with strong inhibitors of P-gp, OCT2, and MATE1/MATE2K drugs. At high dose (e.g., 400 mg BID), ABT-888 may inhibit OCT1 in the liver and MATE1/MATE2K in the kidney.

Veliparib is not a potent inhibitor of the major human CYPs and does not significantly induce activities of major human CYP isoforms, suggesting a negligible potential for CYP-mediated drug-drug interactions as a perpetrator at the anticipated therapeutic concentrations.

In patients, ABT-888 clears primarily in the urine as intact parent drug along with metabolites suggesting that renal function plays an important role in the drug clearance and its metabolites. Drug-associated with kidney toxicities or kidney diseases could change ABT-888 pharmacokinetics. Use caution when administering concomitantly with oxaliplatin, carboplatin, cisplatin, and topotecan in patients with pre-existing renal impairment."

Patient Care Implications: Patients may feel fatigue or tiredness. Loss of appetite and losing weight are common. Provide appropriate supportive care for diarrhea. Avoid long-sun exposure as it might exacerbate skin rash.

9.4.2 MK-3475 (pembrolizumab) (NSC #776864)

- ***Other Names:*** Pembrolizumab, SCH 900475, KEYTRUDA®
- ***Classification:*** Anti-PD-1 MAb
- ***Molecular weight:*** 148.9-149.5 KDa
- ***CAS registry number:*** 1374853-91-4

Mode of Action*:* The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells to suppress immune control. MK-3475 (pembrolizumab) blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands.

Description: MK-3475 (pembrolizumab) is a humanized MAb of the IgG4/kappa isotype.

How Supplied: MK-3475 (pembrolizumab) is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 100 mg vials containing a sterile, non-pyrogenic, clear to opalescent aqueous solution (25 mg/mL). Proteinaceous particles may be present. MK-3475 (pembrolizumab) solution for infusion is formulated in 10mM histidine buffer, pH 5.2-5.8, containing 7% sucrose and 0.02% polysorbate 80, supplied in Type I glass vials with a cap color of red, salmon, or blue.

Preparation: MK-3475 (pembrolizumab) solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of MK-3475 (pembrolizumab) to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final concentration must be between **1 mg/mL to 10 mg/mL**.

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin

Storage: Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box.

If a storage temperature excursion is identified, promptly return MK-3475 (pembrolizumab) to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability testing of the intact vials is on-going**.**

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 20 hours. MK-3475 (pembrolizumab) solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

Route of Administration: IV infusion only. Do not administer as an IV push or bolus injection.

Method of Administration: Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however, if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri-(2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene

Patient Care Implications: Refer to the protocol for information on evaluation and management of potential immune-related adverse events.

Availability: MK-3475 (pembrolizumab) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

MK-3475 (pembrolizumab) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 16.0)

10.0 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

10.1 Specimen Submissions

All patients will be asked to consent to the optional biobanking of biologic samples for future research. ***For patients who agree, sample collection is a protocol requirement.*** Patient samples for all patients will be collected at the specified timepoints outlined in Table 20A. ***Please note that the additional optional collections for patients treated at designated TNT Plus sites (see Table 20B) are no longer to be collected after November 30, 2019.***

Tables 20A and 20B. Summary of patient sample submissions

Table 20A: Sample Submissions for ALL PATIENTS

Sample submissions:	Baseline	During and post mFOLFOX6	During chemoradiation (chemoRT)	Before or at the time of surgery	Post surgery
Archived primary tumor tissue (FFPE)	X[a] *From diagnostic biopsy; must be submitted within 60 days after study entry.*			X[b] At surgery *From surgical resection; must be submitted within 60 days after surgery.*	*(See footnote **d**)*
Whole blood[c]	X *After* randomization; *before* mFOLFOX6 begins	X Within 3 days *before* mFOLFOX6 administration for Cycle 5 **AND** within 3 days *before* starting chemoRT		X Within 14 days *before* surgery	X At 6 month visit, in alignment with repeat imaging

Table 20B: Sample Submission for TNT PLUS SITE PATIENTS ONLY (**As of November 30, 2019, no additional blood or tissue specimens should be obtained.)**

In addition to the sample submissions for "**All patients**," the following tissue and blood samples are to be submitted for patients who are treated at designated TNT Plus Sites and agree to these optional collections:

Sample submissions:	Baseline	During and post mFOLFOX6	During chemoradiation (chemoRT)	Before or at the time of surgery	Post surgery
Fresh tissue	X	X Within 3 days *before* starting chemoRT		X At surgery	
Blood samples	X *After* randomization; *before* mFOLFOX6 begins	X Within 3 days *before* mFOLFOX6 administration for Cycle 5 **AND** within 3 days *before* starting chemoRT	X Week 3 ***AND*** Week 5 only (Arms 1 and 2) ***or*** Week 6 (Arm 3)	X Within 14 days *before* surgery	X 30 days ***AND*** 6 months *after* surgery

Table continued on next page

Tables 20A and 20B. Summary of patient sample submissions *(continued)*

a Submit an archived paraffin block (FFPE) of at least two (2) core biopsy specimens of primary untreated tumor tissue from the diagnostic biopsy.
b Submit an archived paraffin block (FFPE) of surgically resected primary tumor tissue (or residual scar in the setting of pCR).
c Collect three tubes of blood: one (1) 10 mL red/grey top serum separator tube ***and*** one (1) 10 mL purple top tube (EDTA), ***and*** one (1) 10 ml Streck tube at each of these time points during a routine phlebotomy procedure for other standard labs.
d In the event of disease progression/recurrence or diagnosis of a second primary cancer or secondary malignancy, study therapy will be discontinued; however, for patients who agree to the optional biobanking portion of this study, available cancer specimens (FFPE) will be collected through Year 3 from randomization.

Note: Refer to the NRG-GI002 Pathology and Correlative Science Instructions for tumor and blood sample collection, alternative sample submission, processing, and submission instructions.

10.2 Use of specimens

10.2.1 All patients

Any plan to analyze biomarkers collected from patient biospecimens in this protocol, including FFPE and blood samples from patients treated at TNT Plus sites (see Tables 20A and 20B) will be submitted for approval by the NCI CCSC after study closure and before analysis of samples.

In general, the correlative analyses will leverage the annotated clinical data and companion radiographic images (supported through BISQPF 5U10CA180868-03; PI: Wolmark) and assessment of predictors or surrogates of response and resistance. Proposed correlative studies include the association of matched pair tumor samples (baseline and surgical) to identify predictive markers of sensitivity to treatment or potential markers of resistance. Tissue-based assessments will also be characterized and correlated with bioimaging findings such that radiographic surrogacy for treatment response or resistance may be identified. At a minimum, assays to characterize the molecular profile of tumor tissues through NGS and other comprehensive DNA and RNA platforms will be conducted. Additionally, assessment of the immunogenic state of the patient, molecular determinants or evidence of DNA repair deficiency, circulating cell free DNA and circulating tumor cell kinetics, dynamics and correlation with treatment response (all arms) are proposed via exploratory post-hoc, but pre-planned analyses.

- To establish a circulating and tumor-based biomarker program for exploratory secondary analyses related to predicting response across and specific-to novel therapeutic agents.

  Owing to the serial nature of blood and tissue collection and analyses, the TNT platform allows for robust assessment of in-vivo response and biomarker predictors to chemotherapy and chemoradiotherapy response. This can be analyzed both in generic treatment terms as well as for specific modalities (e.g., radiotherapy) and specific novel therapeutic interventions.

  Blood will be collected in appropriate tubes for the assessment of serum, plasma, and buffy coat and will be used for sequencing, cytokine, and biomarker assessment. Blood collection and processing time points will facilitate assessment of baseline, post-treatment and recovery changes in these variables in response to treatment interventions and biologic response modifiers.

Exploratory biomarkers of treatment effect: Relevant to blood collected during chemoRT, DNA Damage Repair proteins, peripheral blood γ-H2AX assay and apoptotic assessments are planned. While there are very few clinical biomarkers available that currently predict response to the agent being actively studied, tumor homologous recombination deficiency (HRD) assessment for patients in the veliparib arm is planned. These biomarkers will be processed and analyzed after study completion in a post-hoc batch manner.

- To determine if genomic signatures can predict local response to chemotherapy and chemoradiotherapy in high-risk rectal adenocarcinoma. This specifically is proposed to include, but may not be limited to, the Radiosensitivity Index (RSI; Cvergenx, Inc.).

  The NCI has recently created the Clinical Assay Development Program (CADP) to foster the commercial development of promising molecular diagnostics that will advance personalized medicine. The Radiosensitivity Index (RSI), a clinically-validated molecular signature of rectal tumor intrinsic radiosensitivity, has been recently selected by NCI for commercial development through this program. In this commercial partnership, the NCI will lead efforts to develop a commercial-grade FDA ready analytically-validated diagnostic platform for RSI. The efforts will focus on developing an FFPE/RT-PCR-based diagnostic platform in rectal cancer. We anticipate that this project will be complete prior to the initiation of this analysis.

  Once the CADP assay is complete, we believe the next step in development is testing the commercial platform for RSI in a multi-institutional collaborative study. Previously obtained FFPE specimens from NSABP R-03 and potentially R-04 are being similarly tested to refine the RSI signature in the rectal cancer patient population. Using baseline specimens obtained in this protocol, the central hypothesis of this correlative subproject is that RSI can be utilized to identify patients with high (high prevalence of complete pathological responders), intermediate (high prevalence of partial pathological responders) and low (low prevalence of any pathological response) likelihood of therapeutic response to preoperative chemoradiation. The development of an accurate approach to identify these three populations would have significant impact on clinical management of patients with rectal cancer. For example, patients that are deemed to have a high probability of complete pathological response might be candidates for non-surgical management. Patients with intermediate and low probability of response might be excellent candidates for studies testing novel therapies or local treatment intensification. Therefore, demonstrating the clinical utility of RSI within a prospective multi-institutional study is of significant clinical importance.

  We intend to categorize patients as high, intermediate, or low likelihood of response based on the RSI score from FFPE tissue using cutoffs that result from the CADP process.

  The TNT platform will support the continued development of tumor-based predictive signatures that may be capable of identifying non-response to standard therapy and serve as an integral biomarker in the future for targeting patients with novel therapies who are at exceptionally high risk for recurrence.

- To determine the effect of FOLFOX and CRT with or without the combination with PD-1 blockade on the density of TILs and T-cell subpopulations in the tumor microenvironment.

- To identify different immune cell populations (effector/memory/ CD8 cells and T regulatory cells) Multiplex ImmunoFluorescence (IF) staining or other relevant technologies may be performed on FFPE tumor slices using the following panels and antibodies: Panel 1 (Cytokeratin (tumor marker), CD4, CD8, CD45RO+cells, FoxP3 and DAP). Panel 2 (Cytokeratin, CD4, CD8, Granzyme B (activation marker) and Ki67 (proliferation marker) and DAPI. Cytotoxic (CD8), memory (CD45RO), and T-regulatory (FOXP3) T cells will be

quantified from the center (CT) and the invasive margin (IM). All Multiplex IF stained slides will be scanned by an automated scanning microscope (Vectra 3, PerkinElmer Inc.) and tumor areas will be marked by a pathologist to exclude non-neoplastic areas, such as stroma, normal epithelial and necrotic regions. Image Analysis will be performed with Inform2.1 image analysis software (PerkinElmer, Inc.) and scoring will be confirmed manually by a pathologist. Immune score will be calculated the center (CT) and the invasive margin (IM) as described before (Pages 2009; Galon 2006). The ratio of effector CD4 and CD8 T-cells/T-regs will be also analyzed.

- To determine the effect of FOLFOX and CRT with or without the combination with PD-1 blockade on PD-L1 and other immune checkpoints expression and whether the combination of CRT and MK-3475 (pembrolizumab) can overcome immune editing.

  Multiplex IF using the following Panel (Cytokeratin, PD-L1, TIM3, LAG3 and DAPI) or other relevant technologies may be performed on all samples. All Multiplex IF stained slides will be scanned by an automated scanning microscope (Vectra 3, PerkinElmer Inc.) and tumor areas will be marked by a pathologist to exclude non-neoplastic areas, such as stroma, normal epithelial and necrotic regions. Image Analysis will be performed with Inform2.1 image analysis software (PerkinElmer, Inc.). The Image Analysis software will be used to quantify and assess the percentage of Cytokeratin+ tumor cells that co-express PD-L1, TIM3, or LAG3. Protocols of these antibodies have been optimized, standardized to minimize staining variance (Chen 2013. Tumor will be considered positive if >5% (CD274 or PD-L1). Data will be compared with that of manual counting by a pathologist to exclude tissue artifacts that cannot be recognized by computer image software.

- To determine the effect of chemotherapy (FOLFOX) and CRT with or without the combination with PD-1 blockade on T-cell repertoire in the periphery and correlate these finding with the effect in the tumor microenvironment.

  Peripheral blood mononuclear cells (PBMCs) will be collected from whole blood to assess immune cell populations. Surface staining with a panel of antibodies (CD3, CD4, CD8, CD19, CD25, FoxP3, CD11c, CD83, CD86, CD56) and intracytoplasmatic cytokine staining, followed by flow cytometry will be performed in order to identify different T cell populations, their activation status, myeloid-derived suppressor cells (CD11b, CD14, CD19, CD33, HLA-DR) and the production of different cytokines as well as other immune cell population. Absolute lymphocyte count (ALC) will be monitored. We will specifically analyze changes as a function of treatments for CCR7+/-/CD45RO+ cell populations for both the CD4+ and CD8+ compartments. The following immune cell populations will be detected in PBMCs using specific marker antibodies and flow cytometry gating strategies: Regulatory T cells (CD4+/CD25+/FoxP3+), Effector T cells (CD4+/CD69+), Naïve T cells (CD4+/CD69-), Memory T cells (CCR7+/CD45RO+), CD8 Cytotoxic cells (CD8+/CD3+), Plasmocytoid Dendritic cells (CD123+/CD303+), Myeloid Dendritic cells (CD11c+/CD141+), Natural Killer cells (CD3-/CD56+), Natural Killer T cells (a/bTCR+/NKG2D+), Classic Monocytes (CD14+), and Monocytic Myeloid-Derived Suppressor cells (CD14+/HLADR-). A panel of cytokines and chemokines may be tested in serum using Luminex cytokine assay or other relevant technology. Changes in cytokine production in immune cell subsets as a function of treatment will be determined by ELISA and intracellular cytokine staining. Plasma from heparin treated blood will be collected, aliquoted and stored at -80C. Via Cytokine/Chemokine Multiplex assays, concentration levels will be assessed for up to 50 biomarkers including (but not limited to) the following inflammatory mediators: IL-6, IFNg, TNFa, IL-10, IP-10, IL-1b, CXCL16, VEGF, and Ang1.

The assays will be performed following manufacturer Standard Operating Procedures for each biomarker group panel.

10.2.2 **TNT-Plus patients**

Objectives:

- To establish feasibility in obtaining serial blood and tumor specimens from patients with colorectal cancer across a multi-site NCTN study.

  In conjunction with the NRG Oncology/NCI U10 Translational Science Center, we aim to establish a scalable and systematic program to collect, process, analyze and store serial biospecimens collected as part of colorectal cancer clinical trials conducted through NRG Oncology. These specimens will be procured through standard operating procedures, processed in a consistent manner and annotated with clinical data. Centralized quality control checks and operational adjustments will be undertaken to optimize the workflow and translational science capacity of the specimens collected. Best practices and procedures from other disease sites participating in the NRG Oncology U10 TSC will be incorporated, but with specific modifications relevant to colorectal cancer tissue collection. Specific high-volume sites with capacity to conduct these types of required processes will be identified as "TNT Plus" sites and will serve as the core participants for completing this translational objective.

  In addition to demonstrating multisite feasibility for such comprehensive specimen collection as part of an NCTN protocol, the scientific end result of this process will include the capacity to develop patient-derived xenografts and/or cell lines, as well as an integrated colorectal cancer multiplex genome and protein kinome assay. Evaluation of DNA, RNA, and protein markers will be assessed with appropriate technologies. This may necessitate the isolation of DNA, RNA, and protein from these tumor specimens. Alternatively, it may be possible to evaluate DNA and RNA utilizing tumor lysates. Currently, HTG Molecular Diagnostics and Nanostring are able to assess RNA levels utilizing tissue lysates. HTG Molecular plans to launch a test for DNA analysis with their technology. These specimens will undergo DNA and protein analysis with possible analysis in the future of the transcriptome and the immune microenvironment. Through subsequent studies, we plan to assess serial tissue and cell-free circulating tumor mutational and proteomic expression changes associated with treatment, recovery and clinical outcomes.

10.3 **Specimen submissions**

All sites – refer to the NRG-GI002 Pathology and Correlative Science Instructions for complete tumor and blood sample collection and submission procedures for all patients.

11.0 **MODALITY REVIEWS**

The Radiation Therapy Co-Chair will perform an RT Quality Assurance Review after IROC-Philadelphia has received complete data. These reviews will be completed remotely and will be ongoing. The final cases will be reviewed within 6 months after this study has reached the target accrual or as soon as IROC-Philadelphia RT has received complete data for all cases enrolled, whichever occurs first. The scoring mechanism is:

Per Protocol; Acceptable Variation; and Unacceptable Deviation.

12.0 ASSESSMENT OF EFFECT

12.1 Clinical complete response (cCR)

12.1.1 Timing of assessments

For the purposes of this study, patients must have a formal perioperative assessment documenting clinical response of the primary rectal tumor via digital rectal exam (DRE) ***and*** proctoscopic or sigmoidoscopic exam. DRE and proctoscopic or sigmoidoscopic exam may be done immediately before surgery.

12.1.2 Definition of cCR

No visible or palpable rectal tumor on direct examination. Nodes are not included in this definition.

12.2 Pathologic complete response (pCR)

12.2.1 Timing of assessments

Presence or absence of pCR will be determined following gross and microscopic examination of tissue removed at the time of surgery according to methods outlined in Section 12.2.2.

12.2.2 Definition of pCR

No histologic evidence of invasive tumor cells in the surgical specimen at the site of the primary tumor and associated regional lymph nodes.

Accurate and uniform assessment of radial margins and pCR is critical for optimal evaluation of GI002 endpoints. Forms must be completed accurately (preferably by the pathologist) and submitted with the surgical pathology report. Specimen processing and pathology examination should follow the *Protocol for the Examination of Specimens from Patients with Primary Cancer of the Colon and Rectum* (Washington 2009). Pathologic tumor (T) and nodal (N) stage along with proximal, distal, and circumferential margin status must be assessed as recommended by CAP in the "Explanatory Notes" section of the CAP protocol.

12.3 Central review

While central review of tumor tissue is not required at this time, pathology specimens should be easily accessible should central review be required in the future. Submission of MRI imaging collected as part of staging or treatment monitoring is required (see Section 8.3.2).

13.0 DOCUMENTATION OF RECTAL CANCER PROGRESSION/RECURRENCE AND OTHER CANCER EVENTS

The diagnosis of a rectal cancer progression *(before surgery)* or recurrence *(after surgery)* should be made only when the clinical and laboratory findings meet the criteria of "acceptable" as defined below. Any progression/recurrence of malignant disease should be proven by biopsy whenever possible.

At the time of rectal cancer progression/recurrence, the investigator should indicate the site of tumor progression/recurrence and whether multiple sites are involved.

Supporting documentation must be submitted with the GI002 Follow-up folder in Medidata Rave following diagnosis of rectal cancer progression/recurrence or invasive second cancer. The documentation will be reviewed at the NRG Oncology SDMC to determine the method(s) used to document the progression/recurrence, the anastomotic location(s) of the progression/recurrence, and the type of second cancer.

13.1 Abdominal and/or pelvic sites

13.1.1 Anastomotic

Acceptable: positive cytology or biopsy

13.1.2 Abdominal, pelvic, and retroperitoneal nodes

Acceptable: positive cytology or biopsy; progressively enlarging node(s) as evidenced by two CT or MRI scans separated by at least a 4-week interval; ureteral obstruction in the presence of a mass as documented on CT or MRI scan; or a single CT or MRI scan showing a definite mass which is confirmed to be malignant by a positive PET scan at that site.

13.1.3 Peritoneum (including visceral and parietal peritoneum or omentum)

Acceptable: positive cytology or biopsy; progressively enlarging intraperitoneal *solid* mass as evidenced by two CT or MRI scans separated by at least a 4-week interval; or a single scan confirmed to be malignant by a positive PET scan at that site.

13.1.4 Ascites

Acceptable: positive cytology

13.1.5 Liver

Acceptable: positive cytology or biopsy or *three* of the following that are not associated with benign disease:

- recent or progressive hepatomegaly, abnormal liver contour;
- positive radionucleotide liver scan, or sonogram;
- positive CT scan or MRI scan;
- positive PET scan which confirms abnormal CT scan or MRI scan and is associated with a rising CEA;
- abnormal liver function studies; or
- elevated CEA, i.e., a persistent rise in CEA titer of 10 times the upper normal value, confirmed on two determinations separated by a 4-week interval, in patients who had a normal postoperative CEA value (the determination should be performed by the same laboratory, using the same method).

Note: An elevated CEA level will, as a solitary finding, not be considered acceptable evidence of rectal cancer progression/recurrence. Non-protocol therapy will not be instituted on the basis of an abnormal CEA level. It is suggested that when CEA elevations occur without other corroborative evidence of rectal cancer progression/recurrence (hepatomegaly, elevated liver function studies, positive radionucleotide scans, etc.), the following investigation should be considered: contrast and/or endoscopic exam; abdominal and pelvic CT scan, sonogram, MRI scan, PET scan, or CEA scan; and/or celiac and mesenteric arteriography. Documentation of corroborative evidence by biopsy is strongly recommended.

13.1.6 Pelvic mass not otherwise specified (NOS)

Acceptable: positive cytology or biopsy; progressively enlarging intrapelvic *solid* mass as evidenced by two CT or MRI scans separated by at least a 4-week interval; or a solid mass on a single CT scan confirmed by a positive PET scan at that site.

13.1.7 Abdominal wall, perineum, and scar

Acceptable: positive cytology or biopsy

13.2 **Nonabdominal and nonpelvic sites**

13.2.1 Skeletal

Acceptable: For all suspected bone-only recurrences/progression, a biopsy is required to demonstrate progression/recurrence.

13.2.2 Lung

Acceptable: positive cytology, aspirate, or biopsy or radiologic evidence of multiple pulmonary nodules that are felt to be consistent with pulmonary metastases.

NOTE: If a solitary lung lesion is found and no other lesions are present on lung tomograms, CT, or MRI scan, further investigations such as biopsy, needle aspiration, or resection should be performed. Proof of neoplastic pleural effusion should be established by cytology or pleural biopsy.

13.2.3 Bone marrow

Acceptable: positive cytology, aspirate, biopsy, or MRI scan

13.2.4 Central nervous system

Acceptable: positive CT or MRI scan, usually in a patient with neurologic symptoms, or biopsy or cytology (for a diagnosis of meningeal involvement).

13.3 **Secondary malignancy**

S***econdary malignancy*** is defined as a cancer that is caused by a treatment for previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. The diagnosis of a secondary malignancy must be confirmed histologically. Representative slides are not required unless requested by the NRG Oncology SDMC for review.

13.4 Second primary cancer

Second primary cancer is defined any ***invasive*** non-rectal cancer other than squamous or basal cell carcinoma of the skin. The diagnosis of an invasive second cancer must be confirmed histologically whenever possible. Representative slides are not required unless requested by the NRG Oncology SDMC for review.

13.5 Documentation requested following death

- Autopsy reports should be secured whenever possible and should be submitted to the NRG Oncology SDMC.
- A copy of the death certificate should be forwarded to the NRG Oncology SDMC if it is readily available or if it contains important cause-of-death information not documented elsewhere.
- Please submit the last clinic/office note before the death or the physician's note summarizing the death.

14.0 DATA AND RECORDS

14.1 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
  - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
  - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
  - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are

available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

14.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave. Additionally, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. See Sections 7.4 and 7.5 for information about adverse event reporting.

Summary of Data Submission: Refer to the CTSU Member website for the table of Required Forms and Materials.

See Section 8.3 for TRIAD account access and installation instructions.

14.3 Global Reporting /Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov).

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design

This is a prospective randomized phase II open label (not blinded) trial. Patients will be randomized with equal allocation (1:1:1) among each of the trial arms. The primary analysis will compare each experimental arm to the concurrently randomized control arm patients.

Patients will be allocated to treatments by a permuted block randomization algorithm with varying block size. Stratification factors include clinical tumor stage (T1 or T2; T3; T4) and clinical nodal stage (N0; N1; N2).

15.2 Primary Endpoint

To demonstrate an absolute improvement in Neoadjuvant Rectal Cancer (NAR) score for the experimental regimen as compared to concurrently randomized control patients.

15.3 Secondary Endpoints

15.3.1 To compare overall survival (OS)

15.3.2 To compare disease-free survival (DFS, time to recurrence, second primary cancer or death)

15.3.3 To compare the rate of pathologic complete response (nodes and tumor), ypT0 and ypN0

15.3.4 To compare the rate of sphincter preservation

15.4 Tertiary Endpoints

15.4.1 To compare the proportion of patients who have a tumor resection overall, conditional on beginning induction chemotherapy, and conditional on beginning chemoradiotherapy

15.4.2 To compare time from initiation of chemoradiotherapy to surgery in the subset of patients with tumor resection

15.5 Exploratory Endpoints

15.5.1 To estimate the rate of disease progression during chemotherapy (prior to chemoradiation)

15.5.2 To compare the rate of clinical complete response rate (cCR), ycT0

15.5.3 To compare the rate of negative circumferential margin

15.5.4 To compare the rate of completion of all cycles of neoadjuvant chemotherapy

15.5.5 To compare the rate of completion of full course of chemoradiation

15.5.6 To compare the toxicity and safety between interventions

15.5.7 To explore the correlative molecular predictors of response and distant failure

15.5.8 To explore the relationship between radiographic findings and pathologic outcomes

15.6 Primary Hypothesis

The experimental arm will have reduced (improved prognosis) NAR score as compared to the control arm.

15.6.1 Power Justification

[redacted]

[redacted]

15.6.2 Expected Sample Size and Accrual Estimates

Eighty-seven (87) patients per arm are required for a study total between 320 and 348 patients, given that the study has already accrued 144 patients to Arms 1 and 2 (as of 20Dec2017). The control arm will be temporally and numerically expanded to account for the addition of Arm 3 (MK-3475 [pembrolizumab]). The control arm will include an equal number of concurrently randomized patients to compare with the new experimental arm. Thus, there could be anywhere from 59 to 87 additional control patients required depending on the temporal overlap in accrual of the two experimental arms.

We anticipate no accrual during a four month start-up phase followed by 14 months of level accrual of 13 patients per month for an eighteen month duration of accrual for the first experimental arm (ABT-888 [veliparib]). The addition of the third arm will result in a temporary suspension of accrual anticipated to last 1 month. The definitive analysis comparing NAR scores for the experimental arms to the control arm should occur 2 to 2.5 years after initiation of each respective experimental arm.

15.7 **Statistical Analyses**

15.7.1 Analyses of Data on the Primary Endpoint

The analysis set is all patients who begin chemoradiotherapy. Patients will be analyzed according to their assigned treatment regardless of treatment actually received. Each experimental arm will be compared to concurrently randomized patients from the control arm for the primary endpoint of NAR score in a linear regression model that controls for the stratification factors (cT-Stage and cN-Stage). Mean NAR scores along with standard errors and confidence intervals will be reported by treatment.

15.7.2 Analyses of Data on Secondary Efficacy Endpoints

Many of the secondary endpoints will be available for reporting immediately following definitive surgery along with the primary endpoint. We anticipate the primary manuscript of each experimental arm will include these endpoints. Most of these endpoints are binary in nature and will be analyzed by a logistic regression model that controls for the stratification factors (cT-Stage and cN-Stage). Observed proportions along with confidence intervals will be presented by treatment.

The time-to-event endpoints of DFS and OS will require additional follow-up beyond surgery and we expect these endpoints will be presented in a second manuscript approximately 3 years after the initial results. These endpoints will be analyzed using the stratified log rank test with strata cT-Stage and cN-Stage. Kaplan-Meier plots will illustrate the distribution of these endpoints by treatment. Cox regression models will be used to estimate hazard ratios and associated confidence intervals. Exploratory analyses of specimens collected will be conducted after review and approval by NCI CCSG.

15.7.3 Analyses of Data on Tertiary Endpoints

The proportions of patients overall (and conditional on beginning induction chemotherapy, and conditional on beginning CRT) will be analyzed by a logistic regression model that controls for the stratification factors (cT-Stage and cN-Stage). Observed proportions along with confidence intervals will be presented by treatment.

Time to surgery (TTS) from initiation of CRT will be analyzed using the stratified log rank test with strata cT-Stage and cN-Stage. Kaplan-Meier plots will illustrate the distribution of TTS by treatment. Cox regression models will be used to estimate hazard ratios and associated confidence intervals.

15.8 **Study Monitoring**

15.8.1 Interim Monitoring of the Primary Objective

There will be interim futility analyses for each experimental arm when (experimental arm and control) 80 patients are evaluable for NAR. Observed NAR score in the experimental arm must be less than the score observed in the control arm (Wieand 1994); otherwise, the Data Monitoring Committee (DMC) will consider a recommendation to close the study early. Since this is purely a futility analysis, no alpha is spent.

15.8.2 Monitoring of Patient Accrual

The NRG Oncology DMC will review the study twice a year with respect to patient accrual.

15.8.3 Monitoring of Protocol Treatment

The NRG Oncology DMC will review the study twice a year with respect to compliance with assigned therapy.

15.8.4 Further Monitoring

The NRG Oncology DMC will review morbidity, serious adverse events, and loss to follow-up. We expect that the annual loss to follow-up is at most 2%. If the annual follow-up is more than 2% at 3 years or more after the initiation of this study, we will study the loss to follow-up data, identify possible causes, and take actions to reduce loss to follow-up.

Additionally, if the rate of disease progression during neoadjuvant chemotherapy ever exceeds 10% of current patient enrollment (evaluated monthly beginning when 30 patients are on trial), further trial enrollment will be held pending evaluation and formal analysis of clinical outcomes and safety. The NRG Oncology DMC also will review the study on an "as needed" basis.

15.9 Secondary Elements

15.9.1 Evaluation of Potential Prognostic and Predictive Markers

Cox regression models will be used to evaluate clinical or histopathologic markers for time-to-event variables. Logistic regression models will be used for binary variables. Models will control for stratification factors and possibly other prognostic variables (e.g. gender or treatment).

15.10 Gender/Ethnicity/Race Distribution

Possible racial and ethnic variation assuming 348 patients are randomized:

The prognostic effect of race/ethnicity will be evaluated using statistical models. Unfortunately, because of power limitations, we will not be able to compare effects separately for the different cultural or racial groups.

Table 21. Gender/Ethnicity/Race Distribution

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	3	2	0	0	5
Asian	3	6	0	0	9
Native Hawaiian or Other Pacific Islander	2	1	0	0	3
Black or African American	6	10	0	0	16
White	104	187	5	10	306
More Than One Race	3	6	0	0	9
Total	121	212	5	10	348

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More Than One Race	0	0	0	0	0
Total	0	0	0	0	0

16.0 COLLABORATIVE AGREEMENTS

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company (ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). -Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

17.0 **REFERENCES**

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Appendix A

ASSESSMENT OF PERFORMANCE STATUS AND ACTIVITIES OF DAILY LIVING

1.0 PERFORMANCE STATUS

ECOG or Zubrod Scale		Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90-100%
1	Restricted in physically strenuous activity but ambulatory	70-80%
2	Ambulatory and capable of self-care; but unable to carry out any work activities	50-60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30-40%
4	Completely disabled	10-20%

2.0 ACTIVITIES OF DAILY LIVING

The following definitions for activities of daily living (ADL) should be used when the current CTCAE version (v4.0 until 3/31/18 or v5.0 beginning 4/1/18) grading criteria are based on ADL:

- *Instrumental ADL* refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- *Self-care ADL* refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

APPENDIX B

CLINICAL MANAGEMENT OF DIARRHEA

Pharmacologic diarrhea management

- For patients with persistent grade 1 diarrhea on loperamide, diphenoxylate hydrochloride and atropine sulfate (Lomotil®) 1 tablet every 6 to 8 hours may be added.
- For ≥ grade 2 diarrhea despite intensive antidiarrheal therapy, consider adding octreotide (short acting) 150 micrograms subcutaneous injection as needed up to three times per day; or after the initial dose of short acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg IM.
- For grade 3 or grade 4 diarrhea with complicating features (dehydration, fever, and/or grade 3-4 neutropenia)
  - Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (< 4 stools/day).
  - Administer octreotide (100-150 µg SC BID or [25–50 µg/hr IV if dehydration is severe, with dose escalation up to 500 µg SC TID).
  - Use IV therapy as appropriate.
  - Stool cultures should be done to exclude infectious causes of grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3 or 4 neutropenia) per the Investigator's discretion. Positive results from occult blood, fecal leukocyte stain, *Clostridium difficile, Campylobacter, Salmonella, and Shigella* testing, if performed, must be reported using the appropriate eCRF.
  - Consider prophylactic antibiotics as needed (e.g., fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or grade 3-4 neutropenia.
- Patients should be monitored for constipation and prophylaxis adjusted accordingly. Do not discontinue antidiarrheals completely; doses may be adjusted.
- For the second and subsequent cycles, the dose of loperamide should be titrated to keep diarrhea controlled to < 4 stools a day.

Dietary management

Instruct patients to:

- Stop all lactose-containing products (milk, yogurt, cheese, etc.).
- Drink 8-10 large glasses (64-80 ounces) of clear liquids per day.
- Eat frequent small meals.
- Maintain a low fat diet enriched with rice, bananas, and applesauce, and/or toast.

APPENDIX C

CREATININE CLEARANCE CALCULATION (COCKROFT-GAULT FORMULA)

Creatinine clearance must either be measured or estimated using the Cockroft-Gault formula, as follows:

For Women

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

or

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85}{815 \times \text{serum creatinine (mmol/L)}}$$

For Men

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

or

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{815 \times \text{serum creatinine (mmol/L)}}$$

APPENDIX D

LEVOLEUCOVORIN DRUG DOSE AND ADMINISTRATION INSTRUCTIONS

Levoleucovorin can be substituted for racemic leucovorin (leucovorin) throughout this protocol, per institutional practice or as needed for drug availability.

Dose:

Levoleucovorin **200 mg/m^2**
(Note: The levoleucovorin dose is one-half the dose of leucovorin.)

Reconstitute as described in the manufacturer's full prescribing information. Do not round the dose.

Administration:

Further dilute the reconstituted levoleucovorin dose with 250 mL D5W.

Using separate infusion bags and separate lines utilizing Y-connector tubing, administer levoleucovorin IV over 2 hours concurrently with oxaliplatin (mFOLFOX6). If oxaliplatin is held, administer levoleucovorin over 2 hours (preferred); however, administration time per institutional practice is permitted.

Due to poor absorption at doses greater than 50 mg, **the use of oral leucovorin is not permitted**.

The decision and rationale for administering levoleucovorin must be documented in the patient's medical record.

Changing the patient's treatment in any way other than as stated above will be considered non-protocol therapy and result in a protocol violation.

APPENDIX E PATIENT DIARY

Protocol: NRG-GI002 / Group 1 and Group 3 **Study Medication: Capecitabine**

Week #_____ of Radiation Therapy (RT)

Prescribed dose: capecitabine _____mg twice each day of RT

- Please record information daily.
- Use a new page for each week of RT.
- You will receive RT 5 days/week (usually not on weekends or holidays). Take capecitabine twice daily **only** on the days that you receive RT.
- Take capecitabine in the morning and evening (within 30 minutes after eating breakfast and dinner).
- Please remember to bring this diary (all pages) and your capecitabine containers (even if they are empty) to each visit with your study team.

Day	Date	Time taken		Number of capecitabine tablets taken (morning)		Number of capecitabine tablets taken (evening)		Notes
		Morning	Evening	150mg	500mg	150mg	500 mg	Include any side effects that you are having (especially loose stools and any medications that you took for the side effects. If you did not receive RT on a regularly scheduled day, record the reason here.
Mon.								
Tues.								
Wed.								
Thurs.								
Fri.								
Sat.								
Sun.								

Patient's name: _____ Date: _____

Physician's office will complete this section:

Total number of capecitabine tablets taken this reporting period: 150 mg _____; 500 mg _____

Total number of capecitabine tablets returned this reporting period: 150 mg _____; 500 mg _____

Research Staff Signature/Date: _____

APPENDIX E PATIENT DIARY

Protocol: NRG-GI002 / Group 2 **Study Medications: Capecitabine and Veliparib**

Week # **of Radiation Therapy (RT)**

Prescribed dose: capecitabine _____mg twice each day of RT *and*
veliparib _____mg twice each day

- Please record information daily. Use page 1 to record capecitabine; use page 2 to record veliparib.
- Use new pages for each week of RT.
- You will receive RT 5 days/week (usually not on weekends or holidays). Take capecitabine twice daily **only** on the days that you receive RT. Take veliparib twice daily **every** day (even on the days that you to not receive RT).
- Take capecitabine in the morning and evening (within 30 minutes after eating breakfast and dinner). Veliparib can be taken with capecitabine. On the days that you do not take capecitabine, veliparib can be taken with or without food.
- Please remember to bring this diary (all pages) and your capecitabine and veliparib containers (even if they are empty) to each visit.

Day	Date	Time taken		Number of capecitabine tablets taken (morning)		Number of capecitabine tablets taken (evening)		Notes
		Morning	Evening	150mg tablets	500mg tablets	150mg tablets	500 mg tablets	Include any side effects that you are having (especially loose stools) and any medications that you took for the side effects. If you did not receive RT on a regularly scheduled day, record the reason here.
Mon								
Tues								
Wed								
Thurs								
Fri								
Sat	Take capecitabine only on the days that you receive RT.							
Sun								

Patient's name: _____ Date: _____

Physician's office will complete this section:

Total number of capecitabine tablets taken this reporting period: 150 mg _____; 500 mg _____

Total number of capecitabine tablets returned this reporting period: 150 mg _____; 500 mg _____

Research Staff Signature/Date: _____

(Group 2 Patient Diary is continued on page 2)

APPENDIX E: PATIENT DIARY

Protocol: NRG-GI002/Group 2 Veliparib				**Study Medication: Capecitabine and**		
Week #		**of Radiation Therapy (RT)**				
Day	**Date**	**Time taken**		**Number of veliparib capsules taken (morning)**	**Number of veliparib capsules taken (evening)**	**Notes**
		Morning	**Evening**	**100mg capsules**	**100mg capsules**	**Include any side effects that you are having (especially loose stools and any medications that you took for the side effects. If you did not receive RT on a regularly scheduled day, record the reason here.**
Mon						
Tues						
Wed						
Thurs						
Fri						
Sat						
Sun						

Patient's name: _____ Date: _____

Physician's office will complete this section:

Total number of veliparib capsules taken this reporting period: _____

Total number of veliparib capsules returned this reporting period: _____

Research Staff Signature/Date: _____

APPENDIX F: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. Please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug **ABT-888 (veliparib)**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

ABT-888 (veliparib) interacts with certain transporter proteins that help move drugs in and out of cells.

The proteins in question are ***OCT2, MATE1, MATE2K, and P-gp.*** ABT-888 (veliparib) is a substrate of P-gp, OCT2, and MATE1/2K and may be affected by other drugs that inhibit these protein transporters. ABT-888 is an inhibitor of OATP1B1, OATP1B3, MATE1/2K, OAT1/3and OCT1 and may affect transport of other drugs in and out of cells.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

ABT-888 (veliparib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors about any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Use caution when administeringABT-888 (veliparib) with other medicines that need certain **transport protein to be effective or to be cleared from your system.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors" of ***P-gp, OCT2, and MATE1/2K.***

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference for a list of drugs to avoid or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____
  He or she can be contacted at _____.

February 2016

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **ABT-888 (veliparib).** This clinical trial is sponsored by the NCI**.** **ABT-888 (veliparib)** may interact with drugs that need certain transport proteins in your body.

Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Use caution as ABT-888 (veliparib) may interact with medicines that stop transport proteins **MATE1/2K, OCT2, and P-gp** to process further in the body**.**

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of P-gp, MATE1/2K, and OCT2.**"
- Before prescribing new medicines, your regular prescribers should go to a frequently updated medical reference for a list of drugs to avoid or contact your study doctor.
- Your study doctor's name is:

_____

Your study doctor can be contacted at:

_____

APPENDIX G

RECOMMENDED RADIOLOGY MAGNETIC RESONANCE IMAGING (MRI) PROTOCOL SPECIFICATIONS

The use of magnetic resonance imaging (MRI) for staging and evaluation of rectal adenocarcinoma has become increasingly predominant in clinical practice. Moreover, recent innovations in MRI technology allow for evaluation of different functional tissue properties with diffusion weighted imaging (DWI). These DWI metrics correlate with the development of a pathologic complete response. The routine use of MRI in NRG-GI002 will provide an exceptional opportunity to better characterize the radiographic changes that correlate with the pathologic response.

MRI imaging of the pelvis to assess clinical T stage and subsequent downstaging is the preferred method for local serial imaging in this study. The details related to MRI image acquisition for 1.5 and 3 Tesla (T) systems are provided in the following tables. These are considered strong recommendations only, but represent imaging standards consistent with expert opinion and are required or otherwise strongly recommended in other active clinical trials of rectal cancer. Of note, with these rectal MRI's, pelvic phased array coils should be used, not endorectal coils. DCE components of the images below are included for reference only and are optional acquisition phases. Finally, it is strongly recommended that patients are imaged using the same strength MRI scanner for all of their rectal MRI's.

G.1: Recommended MRI protocol specifications for 1.5 T system

Sequences	1	2	3	4	5*	6	7	8	9
Series Descriptor	Axial T2	Coronal T2	Sagittal T2	Oblique Axial T2	Oblique Coronal T2	DIFFUSION	3D T1 pre	Sagittal DCE perfusion pre & post	3D T1 post
Generic sequence name	FRFSE T2	FRFSE T2	FRFSE T2	FRFSE T2	FRFSE T2	2D	LAVA	3D FSPGR	LAVA
Plane	Axial	Coronal	Sagittal	Oblique Axial	Oblique Coronal	Axial	Axial	Oblique through tumor	Axial
Options	Fast/NPW /ED	Fast/ NPW /ED	Fast/ NPW /ED	Fast/NPW /ED	Fast/NPW /ED	EPI, DIFF	ZIPX2/ACC /ED	Fast/NPW/EDR /MPh/zip off	ZIPX2/ACC /ED

Continued on next page

G.1: Recommended MRI protocol specifications for 1.5 T system *(continued)*

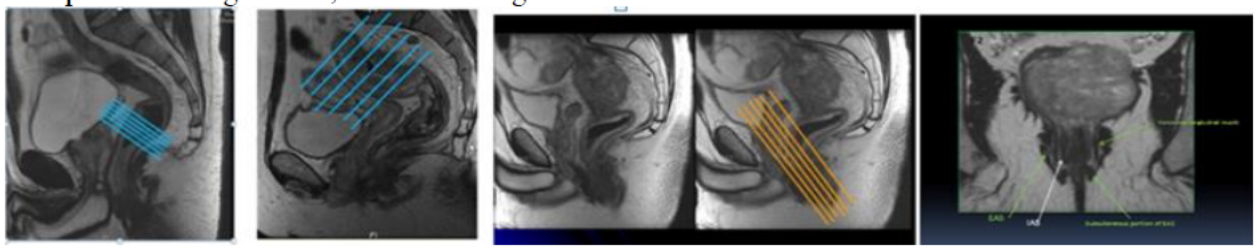
Field of View (cm)	18-26	18-26	18-26	18-26	18-26	28-36	28-36	24	28-36
Slice Thickness (mm)	5	4	4	3	3	5	3	5	3
Gap (mm)	1	1	1	1	1	1	NA	0	NA
Saturation Pulse	S/I/A	N/A	A	S/I/A	A	N/A	DEFAULT	N/A	DEFAULT
TE1 / TE2	102	102	102	102	102	Min	IN PHASE	Min	IN PHASE
TR	4000-6000	4000-6000	4000-6000	4000-6000	4000-6000	3500	DEFAULT	4	DEFAULT
Flip Angle	90	90	90	90	90	N/A	15	30	15
Bandwidth (kHz)	32	32	32	32	32	N/A	62	62.5	62
ETL	24	24	24	24	24	na		na	
NEX	3	3	3	3	3	6	1	1	1
Phase Encoding Steps	192	192	192	192	192	128	192	128	192
Frequency Steps	320	320	320	320	320	128	320	256	320
Frequency Direction	A/P	S/I	R/L	R/L	R/L	A/P	R/L	R/L	R/L

Continued on next page

G.1: Recommended MRI protocol specifications for 1.5 T system *(continued)*

Comments:	breath hold	non breath hold	non breath hold	non breath hold	non breath hold	b=400, directions all	breath hold	1 phase inject delay 16 locs/40 phases	breath hold
	Cover entire pelvis thru sphincter, pelvic nodes and bifurcation				Go thru anal sphincter	b=800, directions all	Cover entire pelvis thru sphincter, pelvic nodes and bifurcation	1 phase < 10 sec	Cover entire pelvis thru sphincter, pelvic nodes and bifurcation
								CV6-Turbo Mode = 2	

*Sequence 5 through tumor:
Oblique cuts through tumor, if tumor is long and curves do several re-oriented slabs.



Continued on next page

G.2: Recommended MRI protocol specifications for 3 T system

Sequences	1	2	3	4	5*	6	7	8	9
Series Descriptor	Axial T2	Coronal T2	Sagittal T2	Oblique Axial T2	Oblique Coronal T2	DWI	Axial 3D T1 pre	Sagittal DCE perfusion pre & post	Axial 3D T1 post
Generic sequence name	FRFSE T2	FRFSE T2	FRFSE T2	FRFSE T2	FRFSE T2	DWI	LAVA	3D FSPGR	LAVA
Plane	Axial	Coronal	Sagittal	Oblique Axial	Oblique Coronal	Axial	Axial	Oblique through tumor	Axial
Options	Fast/NPW /ED	Fast /NPW /ED	Fast NPW /ED	Fast/ /NPW /ED	Fast/NPW /ED	EPI, b0, b400,b800 Directions All	breath hold	Fast, EDR, MP, PFF	breath hold
Field of View (cm)	16-24	16-24	16-24	16-24	16-24	Match T2 Axial	28-36	24-32	28-36
Slice Thickness (mm)	5	4	4	3	3	5	3	5	3
Gap (mm)	1	1	1	1	1	1	NA	0	NA
Saturation Pulse	S/I/A	NA	A	S/I/A	A		DEFAULT		DEFAULT
TE1 / TE2	120	120	120	120	120	80	IN PHASE	Minimum	IN PHASE
TR	4000-6000	4000-6000	4000-6000	4000-6000	4000-6000	3500	DEFAULT	Minimum	DEFAULT
Flip Angle	90	90	90	90	90	90	15	30	15
Bandwidth (kHz)	32	32	32	32	32	NA	62	Variable	62
ETL	23	23	23	23	23				
NEX	4	4	4	4	3	4	1	S/I	1

Continued on next page

G.2: Recommended MRI protocol specifications for 3 T system *(continued)*

Phase Encoding Steps	224	224	224	224	224	128	192	192	192
Frequency Steps	320	320	320	320	320	128	320	288	320
Frequency Direction	A/P	S/I	R/L	R/L	R/L	R/L	R/L	Perfusion	R/L
Comments:	non breath hold	non breath hold	non breath hold	non breath hold	non breath hold	breath hold	breath hold	1 phase inject delay 16 locs/40 phases	breath hold
	Cover entire pelvis thru sphincter, pelvic nodes and bifurcation				Go thru anal sphincter	Create ADC Map	Cover entire pelvis thru sphincter, pelvic nodes and bifurcation	1 phase < 10 sec CV6-Turbo Mode = 2	Cover entire pelvis thru sphincter, pelvic nodes and bifurcation

*Sequence 5: Oblique cuts through tumor- if tumor is long and curves do several oriented slabs: