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NRG-GI008: COLON ADJUVANT CHEMOTHERAPY BASED ON EVALUATION OF RESIDUAL DISEASE (CIRCULATE-NORTH AMERICA)

ClinicalTrials.gov Identifier NCT# 05174169
NCI Version Date: September 25, 2023

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ALLIANCE / Alliance for Clinical Trials in Oncology
CCTG/Canadian Cancer Trials Group
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG

Participating Sites
☒ U.S.
☒ Canada
☐ Approved International Member Sites

Document History	
Amendment #2	September 25, 2023
Amendment #1	June 14, 2023
Pre-activation Revision	February 01, 2022
Initial	September 08, 2021

Protocol Agents:

Agent	Supply	NSC#	IND*	IDE#	IDE Sponsor
Oxaliplatin	Commercial	266046	N/A	G210334	Natera™
5-fluorouracil	Commercial	19893			
Leucovorin	Commercial	3590			
Irinotecan	Commercial	61648			
Capecitabine	Commercial	712807			
Levoleucovorin	Commercial	807037			

*This study is exempt from IND Requirements per 21 CFR 312.2(b).

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For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at http://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e., participant 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.		

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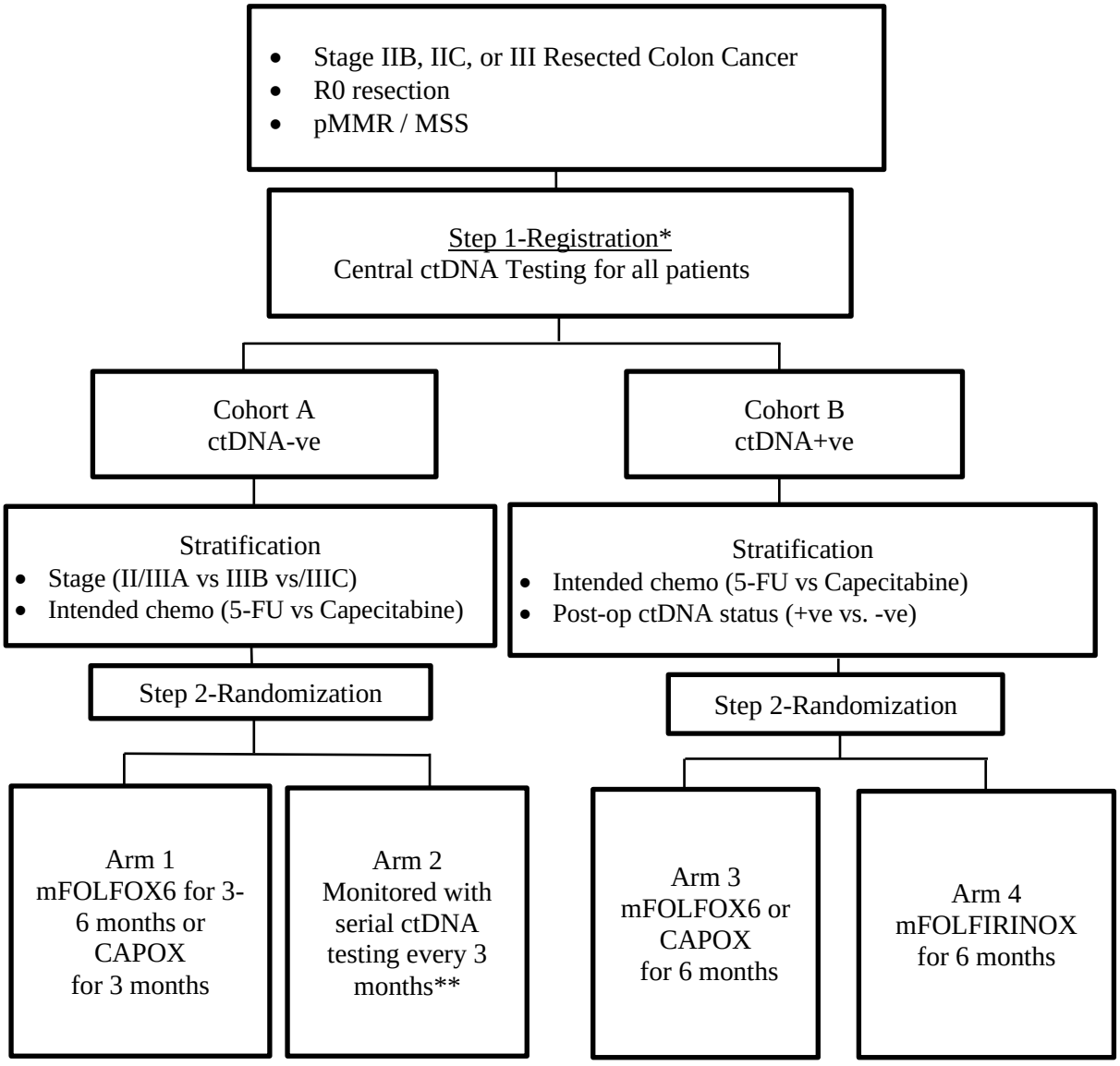
Figure 1.
NRG-GI008 SCHEMA



* For patients on all arms, one cycle of chemotherapy (regimen per treating physicians' discretion – 5-FU or capecitabine with or without oxaliplatin) is allowed but not required after consent. The optional cycle of chemotherapy should be started ≥ 4 weeks from surgery and while awaiting Step 2 randomization. After randomization, refer to the appropriate regimen in Section 5.0.

**Patients in Cohort A (Arm 2) who develop a ctDNA +ve assay during serial monitoring may transition to the ctDNA+ve cohort (Cohort B) and undergo a second randomization.

1.0 OBJECTIVES

1.1 Primary Objective

ctDNA-ve Cohort (Arms 1 + 2):

Phase II: To compare time to ctDNA (+ve) status in ctDNA (-ve) cohort following resection of stage III colon cancer treated with immediate vs delayed (based on serial ctDNA surveillance) chemotherapy. Time to positive event is defined as time from randomization to the first ctDNA positive result for the immediate arm (Arm 1) and to the 2nd ctDNA positive result for the delayed arm (Arm 2) to allow for the potential effect of delayed adjuvant chemotherapy. Patients recurred without a positive ctDNA result will be considered to have ctDNA positive status at the time of recurrence for both study arms.

Phase III: To compare time to DFS event (recurrence, second primary colorectal cancer or death) in ctDNA (-ve) cohort following resection of stage III colon cancer treated with immediate vs delayed (based on serial ctDNA surveillance) chemotherapy.

ctDNA+ve Cohort (Arms 3 + 4):

Phase II and III: To compare time to DFS event (recurrence, second primary colorectal cancer or death) in ctDNA (+ve) cohort following resection of colon cancer treated with 5-FU (or capecitabine) and oxaliplatin x 6 months or 5-FU, oxaliplatin and irinotecan x 6 months.

1.2 Secondary Objectives

1.2.1 To describe the prevalence of detectable ctDNA in patients with stage III colon cancer following surgical resection. The finding will be reported together with the main results of the Phase II portion of the trial.

1.2.2 To estimate time-to-event outcomes (overall survival and time to recurrence) by ctDNA marker status and treatment

1.2.3 To assess the compliance of adjuvant chemotherapy.

1.3 Exploratory Objectives

1.3.1 To explore the kinetics of quantitative ctDNA levels over time and its association with time to event outcomes (RFS, OS, and TTR).

1.3.2 To characterize genomic profiles associated with recurrence using a ctDNA assay in patients with resected colon cancer.

2.0 BACKGROUND

2.1 Introduction

Current NCCN guidelines recommend combination chemotherapy with FP and oxaliplatin for all patients with stage III colon cancer. However, data from historical trials and the ACCENT database suggest that over 40% of the patients are cured by surgery alone and thus do not require adjuvant therapy. Furthermore, with the current standard of care of FP + oxaliplatin, as evident from NSABP-C-07, MOSAIC and IDEA trials, only incremental advances have been made. Based on data from the IDEA trial, three-year DFS of stage III patients treated with current standard of care of FP + oxaliplatin is 75%, ranging from 83% in T1-3N1 to 65% in T4 or N2 disease. Cumulatively, these data suggest that a) not all stage III colon cancer patients require intensive adjuvant therapy and a validated risk stratification method with higher specificity than TNM staging for recurrence is thus required b) current standard of care is inadequate in a subgroup of patients who develop recurrent disease who must be targeted to more intensive therapies.

Arising from tumor cell secretion and apoptosis, ctDNA from release of tumor DNA into the bloodstream is considered a surrogate for minimal residual disease. These somatically mutated tumor DNA fragments can be detected with very high specificity and high sensitivity. Detection of ctDNA following resection of colon cancer has been demonstrated in multiple, independent studies as a strong prognostic biomarker for tumor recurrence. Our trial will provide the first prospective data for the testing of ctDNA as a predictive integral biomarker for response to adjuvant FOLFOX chemotherapy in patients with high-risk stage II (IIB or IIC) and stage III colon cancer. Presence of minimal residual disease (MRD), as defined by the presence of detectable ctDNA, is rapidly emerging as a highly specific marker for disease recurrence post-curative resection. The current concept builds on these data to establish ctDNA as a biomarker for determining intensity of adjuvant therapy in patients with resected high-risk stage II and stage III colon cancer.

Under the trial design, patients with (R0) resected colon cancer will be analyzed for ctDNA defined MRD from a blood sample collected postoperatively no later than 8 weeks within the date of surgical resection (i.e., to allow ctDNA results to return within the accepted 12-week range to initiate adjuvant therapy). Based on discussions with CRC experts, patient advocates, and results of a survey of the Colon Cancer Task Force members, patients with T4 and / or N2 stages were initially excluded from Cohort A (ctDNA negative) to avoid the (small) chance of a false negative post-operative ctDNA assay adversely affecting outcomes in these patients. However, based on the review of emerging data from other studies (see below) by key opinion leaders and patient advocates, these patients will now be allowed for enrollment. In eligible patients, if the ctDNA assay is negative, patients will be randomized between immediate FP + oxaliplatin vs delayed (based on serial ctDNA testing and only if ctDNA+ve) adjuvant chemotherapy. At the time that ctDNA is detected (immediately after surgery or during serial testing), patients will be randomized to receive 6 months of chemotherapy with FP + oxaliplatin or 5-FU or oxaliplatin and irinotecan for 6 months. Plasma samples will be obtained every 3 months while on adjuvant therapy and during surveillance at time of clinic visits an invaluable resource to assess ctDNA kinetics and future biomarkers.

This proposed trial provides important insights into the use of ctDNA as an objective tool to help oncologists identify patients with colon cancer who are high-risk for recurrence and to determine the intensity of adjuvant chemotherapy accordingly. Current guidelines recommend adjuvant chemotherapy with minimal personalized risk stratification. For instance, guidelines recommend that all patients with stage III colon cancer receive adjuvant chemotherapy when in

reality only a proportion (approximately 20-25%) require or benefit from such therapy (elimination of micrometastatic disease with adjuvant therapy resulting in improved long-term survival). Therefore, improved predictive biomarkers are warranted in order to identify patients with colon cancer who may benefit from adjuvant chemotherapy, and alternatively, to identify those who do not benefit and can be spared the otherwise needless toxicity and expense of systemic treatment. Furthermore, ctDNA has the potential to identify patients that are likely to relapse following completion of standard adjuvant therapy and may benefit from intensification of treatment.

Our goal is to provide Level 1 evidence that post-operative ctDNA status can be reliably used to determine intensity of adjuvant chemotherapy in patients with colon cancer. If this study is successful, the absence of ctDNA post-resection would subsequently guide medical oncologists to de-escalate the intensity of adjuvant therapy. Equally importantly, the results will help develop improved standard of care adjuvant regimens for those at high risk of recurrence as identified by presence of ctDNA. In summary, results of this trial would validate ctDNA as an objective assay in clinical decision-making of how to determine the intensity of adjuvant chemotherapy for patients with colon cancer. Results of this study will also help define the role of ctDNA in the staging of patients with colon cancer, potentially leading to incorporation in AJCC staging guidelines. Therefore, the information from the efforts proposed here has the potential to guide the clinical management of colon cancer patients enrolled with detectable and undetectable ctDNA alike.

This trial will also generate important descriptive data regarding the prevalence of ctDNA in patients with resected colon cancer and ctDNA kinetics in these patients during adjuvant therapy and surveillance.

An Australian study (Tie 2016) analyzed 230 patients with stage II colon cancer who had identifiable mutations using a ctDNA NGS panel on blood collected 4-10 weeks after surgical resection. Among the 178 of these patients that did not receive adjuvant chemotherapy, 164 patients had no detectable ctDNA at baseline, while 14 (8.5%) had detectable ctDNA. Three - year recurrence-free survival was 90% in the ctDNA-negative group and 0% in the ctDNA-detectable group (all relapsed). Detectable ctDNA following resection had a positive predictive value of 100% and negative predictive value of 92%. Multivariate analysis of various clinicopathologic risk factors for recurrence showed that the detection of ctDNA was associated with the highest risk for recurrence (HR 28, P<.001), and the only traditionally utilized factor with a significant risk for recurrence was a T4 tumor (HR 8.1, P<.001). Other commonly utilized patient and tumor characteristics (i.e., < 12 lymph nodes examined, presence of lymphovascular invasion, microsatellite status) did not meet statistical significance in this analysis. In the prospective, randomized DYNAMIC trial, 455 patients with resected stage II colon cancer were assigned 2:1 to management based on ctDNA status ("ctDNA-guided") vs standard of care approach ("standard") with a primary endpoint of recurrence free survival at 2 years and a key secondary end point of adjuvant chemotherapy use. After a median follow-up of 37 months, a lower percentage of patients in the ctDNA guided group received adjuvant therapy (15% vs. 28%; relative risk, 1.82; 95% confidence interval [CI], 1.25 to 2.65) and the 2-year recurrence free survival was noninferior (93.5% and 92.4%, respectively; absolute difference, 1.1 percentage points; 95% CI, −4.1 to 6.2 [noninferiority margin, −8.5 percentage points]) (Tie 2022). These data suggest that detection of postoperative ctDNA can serve as both a specific and sensitive tool in quantifying minimal residual disease following resection as a prognostic biomarker.

For patients with resected stages II and III colon cancers, a separate study using the Roche Avenio ctDNA surveillance kit corroborated the use of ctDNA technology as a method to identify patients with colon cancer at high risk for recurrence (Maximilian 2017). Here, 145 patients with R0 resections for colorectal cancer (86 stage II patients and 59 stage III patients) underwent

interrogation using this 197-gene panel for the presence of ctDNA in the blood at a median of 10 days postoperatively. A median of 4 (range, 1-24) somatic variants were detected in 144 of 145 tumors. Detectable ctDNA (N=12, 8.3%) was associated with an inferior RFS (17% vs. 88%, HR 10.3, P < .00001), inferior time to recurrence (HR 20.6, P < .00001), and a shorter overall survival (HR 3.4, P < .00001). The time to recurrence was shorter in the ctDNA (+) patients relative to the ctDNA (-) patients alike for both the stages II and III cohorts (P < .00001). These data validate the previously described Australian findings of detectable ctDNA as a poor prognostic biomarker, here using the Roche Avenio assay.

In a prospective, multicenter Danish study of 125 patients with stages I – III CRC with serial ctDNA evaluated by the Signatera™ assay, patients who were ctDNA(+ve) post-operatively were more likely to relapse than ctDNA(-ve) patients (HR 7.2; 95% CI, 2.7-19; p < 0.001). Monitoring during and after adjuvant chemotherapy suggested that 30% of the patients were cleared and patients who were ctDNA(+ve) after completion of adjuvant therapy had a very high risk of recurrence (HR 17.5; HR, 17.5; 95% CI, 5.4-56.5; *P* < .001) (Reinert 2019). In another Australian study of 100 stage III colon cancer patients, 21% of patients were ctDNA(+ve) post-operatively and were shown to have a higher risk of relapse (HR 3.8; 95% CI, 2.4-21.0; *P* < .001). Post-adjuvant chemotherapy, 17% patients were noted to be still ctDNA+ve with continued higher risk of relapse (HR 6.8; 95% CI, 11.0-157.0; *P* < .001) (Tie 2019). Multivariate analyses in both studies showed that ctDNA status was independently associated with relapse after adjusting for known clinicopathologic risk factors in line with findings of prior studies. Finally, in the above mentioned Danish study, serial ctDNA analysis revealed disease recurrence ahead of time (mean, 8.7 months; range 0.8-16.5 months) with sensitivity 88% and specificity 98% (Reinert 2019) proving the reliability and utility of such monitoring.

The MD Anderson has also demonstrated the detection of ctDNA as a poor prognostic biomarker for recurrence in patients with stage IV colorectal cancer undergoing resection of liver metastases (Overman 2017). Using a 21-gene NGS panel (GuardantHealth), in 54 patients undergoing hepatectomy with curative intent, postoperative detection of ctDNA was associated with an inferior RFS (HR 3.1, P = .002). Recurrence via ctDNA positivity occurred a median of 5.1 months prior to radiographic recurrence.

Results from the ongoing GALAXY study, an observational study evaluated pre- and post-surgery ctDNA utilizing Signatera MRD assay in 1039 patients with stage II-IV colorectal cancer. After a median follow-up of 16.74 months, postsurgical ctDNA detection was associated with a high risk of recurrence (HR 10.0, *P* < 0.0001) and also identified patients who derived benefit from adjuvant therapy (HR 6.59, *P* < 0.0001). Of note, in ctDNA-negative patients, after adjusting for confounding factors, no statistically significant benefit from adjuvant therapy was noted (adjusted HR 1.71, 95% CI 0.80–3.7, *P* = 0.167) with an 18-month disease free survival of 94.9% (95% CI 91.0–97.2%) and 91.5% (95% CI 87.6–94.2%) in the adjuvant and the observation (no-adjuvant therapy) groups, respectively. This study also evaluated ctDNA status change with adjuvant chemotherapy and risk of recurrence. Compared with patients who were persistently negative, a significantly higher risk of recurrence was observed for those who converted from ctDNA negative to positive (HR 14.0, 95% CI 8.5–24.0, *P* < 0.001), with an 18-month DFS of 33.8% (95% CI 18.1–50.2%), and for patients who remained persistently positive (HR 21.0, 95% CI 14.0–31.0, *P* < 0.001), with an 18-month DFS of 22.9% (95% CI 14.3–32.7%) (Kotani 2023).

Collectively, these findings show that in CRC patients: a) post-operative ctDNA status is highly prognostic independent of stage even after adjusting for other known prognostic variables; b) only a proportion of patients who are ctDNA+ve post-operatively clear their ctDNA with adjuvant chemotherapy and continue to be at a very high risk of recurrence; and finally, c) serial ctDNA

monitoring may provide lead-time and reveal disease recurrence ahead of radiographic recurrence with high sensitivity and specificity.

The goal of the current study is to address these deficiencies by determining the intensity of adjuvant chemotherapy based on post-operative and serial ctDNA status. In patients who are ctDNA(-ve) after surgery, we will evaluate whether selective use of adjuvant chemotherapy based on serial ctDNA surveillance is non-inferior to the current approach of treating all such patients with adjuvant therapy irrespective of ctDNA status. Furthermore, acknowledging the limited efficacy of current adjuvant regimens, we aim to improve on the standard of care FP + oxaliplatin by testing the incremental benefit of adding other therapies through two experimental arms. One arm will evaluate the benefit of adding irinotecan to the standard of care FP + oxaliplatin doublet.

3.0 ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Clinical Coordinating Department (CCD [see protocol cover page]).

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

Investigators should check with their site Pathology department regarding release of tumor tissue before approaching patients about participation in the trial.

3.1 Patient Entry and Randomization

The following sections outline procedures for Study Entry and Randomization.

3.1.1 Step 1: Study Entry and ctDNA assay testing.

- The authorized site staff must obtain signed informed consent from the potential patient before any study specific procedures are performed.
- The authorized site staff must determine patient eligibility (with exception of central ctDNA testing) by completing the assessments on Table 1 that are required prior to Step 1/Study entry. See Sections 3.2 and 3.3.
- Step 1 Entry in OPEN: Patients will be assigned a unique patient identifier which will be used to identify the blood and tumor samples to be sent for central Signatera™ ctDNA testing, the eCRFs in Medidata RAVE, and any other trial-related communications.
- Once potential eligibility has been confirmed and consent signed, one cycle of chemotherapy (regimen per treating physicians' discretion – 5-FU or capecitabine with or without oxaliplatin) is allowed but not required after consent. The optional cycle of chemotherapy should be started ≥ 4 weeks from surgery and while awaiting Step 2 randomization. *Note: This optional cycle of chemotherapy is not to be included in the planned duration of the treatment regimen.*

3.1.2 Step 2: Randomization

- Following ctDNA assay testing and receipt of central testing results, the authorized site staff will randomize the patient using OPEN.
- OPEN will randomly assign treatment by cohort (ctDNA-ve or ctDNA+ve).

3.1.3 Second Randomization (Cohort A-Arm 2 patients who convert to ctDNA +ve)

- Cohort A-Arm 2 patients who develop a positive ctDNA assay during serial monitoring will transition to the ctDNA+ ve cohort (Cohort B) and undergo a second randomization to Arm 3 or Arm 4 treatment.
- The authorized site staff must determine patient eligibility (see Section 3.4).
- Patients must reaffirm their willingness to be enrolled in Cohort B and randomized to Arm 3 or 4 after review of the current consent form and signing a reaffirmation form.
- OPEN will randomly assign patient to Arm 3 or Arm 4.

3.2 Eligibility Criteria

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

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

3.2.2 The patient must be ≥ 18 years old.

3.2.3 The patient must have an ECOG performance status of 0 or 1 (see Appendix A).

3.2.4 Patients must have histologically/pathologically confirmed Stage IIB, IIC, or Stage III colon adenocarcinoma with R0 resection according to AJCC 8th edition criteria.

3.2.5 No radiographic evidence of overt metastatic disease within 45 days prior to Step 1/Study entry (CT with IV contrast or MRI imaging is acceptable and **must** include chest, abdomen, and pelvis).

3.2.6 The distal extent of the tumor must be ≥ 12 cm from the anal verge on colonoscopy or above the peritoneal reflection as documented during surgery or on pathology specimen (i.e., excluding rectal adenocarcinomas warranting treatment with chemoradiation).

3.2.7 The patient must have had an en bloc complete gross resection of tumor (curative resection). Patients who have had a two-stage surgical procedure, to first provide a decompressive colostomy and then in a later procedure to have the definitive surgical resection, are eligible.

3.2.8 The resected tumor specimen and a blood specimen from patients with Stage IIB, IIC, or Stage III colon cancer must have central testing for ctDNA using the Signatera assay by Natera (after Step 1/Study entry and before Step 2/Randomization). Patient must have sufficient tissue to meet protocol requirements (See Table 16). This blood specimen for the Signatera assay must be collected after surgery (and recommended at least 14 days post-surgery).

3.2.9 Tumor must be documented as microsatellite stable or have intact mismatch repair proteins through CLIA-approved laboratory testing. Patients whose tumors are MSI-H or dMMR are excluded.

3.2.10 The treating investigator must deem the patient a candidate for all potential agents used in this trial (5FU, LV, oxaliplatin and irinotecan).

3.2.11 The interval between surgery (post-operative Day 7) and Step 1/Study entry must be **no more than 60 days**. Note: Step 1/Study Entry may occur as early as post-operative Day 7, but it cannot occur beyond 60 days from the actual date of the patient's surgery.

3.2.12 Availability and provision of adequate surgical tumor tissue for molecular diagnostics and confirmatory profiling.

3.2.13 Adequate hematologic function within 28 days before Step 1/Study entry defined as follows:

- Absolute neutrophil count (ANC) must be ≥ 1500/mm^3;
    - Participants with benign ethnic neutropenia (BEN): ANC < 1300 mm^3 are eligible.
    - BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestations (Atallah-Yunes 2019). BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups.
- Platelet count must be ≥ 100,000/mm^3; *and*

- Hemoglobin must be ≥ 9 g/dL.

3.2.14 Adequate hepatic function within 28 days before Step 1/Study entry defined as follows:
- total bilirubin must be ≤ ULN (upper limit of normal) for the lab *and*
- alkaline phosphatase must be < 2.5 x ULN for the lab; *and*
- AST and ALT must be < 2.5 x ULN for the lab.

3.2.15 Adequate renal function within 28 days before Step 1/Study entry defined as serum creatinine ≤ 1.5 x ULN for the lab ***or*** measured or calculated creatinine clearance ≥ 50 mL/min using the Cockroft-Gault formula for patients with creatinine levels > 1.5 x ULN for the lab.

For Women

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

For Men

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

Note: Adjusted body weight (AdjBW) should be used for patients that have BMI ≥ 28 (≥30% above IBW).

3.2.16 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.2.17 Pregnancy test (urine or serum according to institutional standard) done within 14 days before Step 1/Study entry must be negative (for women of childbearing potential only).

3.2.18 Patients receiving a coumarin-derivative anticoagulant must agree to weekly monitoring of INR if they are randomized to Arm 1 or Arm 3 and receive capecitabine.

3.3 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Colon cancer histology other than adenocarcinoma (i.e., neuroendocrine carcinoma, sarcoma, lymphoma, squamous cell carcinoma, etc.).

3.3.2 Pathologic, clinical, or radiologic overt evidence of metastatic disease. This includes isolated, distant, or non-contiguous intra-abdominal metastases, even if resected.

3.3.3 Tumor-related bowel perforation.

3.3.4 History of prior invasive colon malignancy, regardless of disease-free interval.

3.3.5 History of bone marrow or solid organ transplantation (regardless of current immunosuppressive therapy needs). Bone grafts, skin grafts, corneal transplants and organ/tissue donation are not exclusionary**.**

3.3.6 Any prior systemic chemotherapy, targeted therapy, or immunotherapy; or radiation therapy administered as treatment for colorectal cancer (e.g., primary colon adenocarcinomas for which treatment with neoadjuvant chemotherapy and/or radiation is warranted are not permitted) Exception: one cycle of chemotherapy (regimen per treating physicians' discretion – 5-FU or capecitabine with or without oxaliplatin) is allowed but not required after consent. The optional cycle of chemotherapy should be started ≥ 4 weeks from surgery and while awaiting Step 2 randomization.

3.3.7 Other invasive malignancy within 5 years before Step1/Study entry. Exceptions are colonic polyps, non-melanoma skin cancer or any carcinoma-in-situ.

3.3.8 Synchronous primary rectal and/ or colon cancers.

3.3.9 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.3.10 Sensory or motor neuropathy ≥ grade 2, according to CTCAE v5.0.

3.3.11 Blood transfusion within two weeks before collection of blood for central ctDNA testing.

3.3.12 Active seizure disorder uncontrolled by medication.

3.3.13 Active or chronic infection requiring systemic therapy.

3.3.14 Known homozygous DPD (dihydropyrimidine dehydrogenase) deficiency.

3.3.15 Patients known to have Gilbert's Syndrome or homozygosity for UGT1A1*28 polymorphism.

3.3.16 Pregnancy or lactation at the time of Step 1/Study entry.

3.3.17 Co-morbid illnesses or other concurrent disease that would make the patient inappropriate for entry into this study (i.e., unable to tolerate 6 months of combination chemotherapy or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens or prevent required follow-up).

3.4 Eligibility Criteria for Cohort A Arm-2 patients on Second Randomization

3.4.1 Patient must have developed a ctDNA +ve assay during serial monitoring.

3.4.2 Patient's willingness to be re-randomized affirmed. (A Reaffirmation Form will be available on CTSU for patients to sign).

3.4.3 The patient must continue to have an ECOG performance status of 0 or 1 (see Appendix A).

3.4.4 No radiographic evidence of overt metastatic disease.

3.4.5 Pregnancy test (urine or serum according to institutional standard) done within 14 days before second randomization must be negative (for women of childbearing potential only).

3.4.6 Adequate hematologic function within 28 days before second randomization defined as follows:

- Absolute neutrophil count (ANC) must be ≥ 1500/mm^3;
    - Participants with benign ethnic neutropenia (BEN): ANC < 1300 mm^3 are eligible.
    - BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestations (Atallah-Yunes 2019). BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups.
- Platelet count must be ≥ 100,000/mm^3; *and*
- Hemoglobin must be ≥ 9 g/dL.

3.4.7 Adequate hepatic function within 28 days before second randomization defined as follows:

- total bilirubin must be ≤ ULN (upper limit of normal) for the lab *and*
- alkaline phosphatase must be < 2.5 x ULN for the lab; *and*
- AST and ALT must be < 2.5 x ULN for the lab.

3.4.8 Adequate renal function within 28 days before second randomization defined as serum creatinine ≤ 1.5 x ULN for the lab ***or*** measured or calculated creatinine clearance ≥ 50 mL/min using the Cockroft-Gault formula for patients with creatinine levels > 1.5 x ULN for the lab.

For Women

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

For Men

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

Note: Adjusted body weight (AdjBW) should be used for patients that have BMI ≥ 28 (≥30% above IBW).

3.5 **Ineligibility Criteria for Cohort A Arm-2 patients on Second Randomization**

3.5.1 Pregnancy or lactation at the time of second randomization.

3.5.2 No longer a candidate for systemic chemotherapy (FOLFOX, CAPOX, and mFOLFIRINOX) in the opinion of the treating investigator.

NIH Participant Population Inclusion Policy

NIH policy requires that participants regardless of gender identity and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Participants of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf

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

Table 1. Tests, exams, and other requirements before study entry and before randomization

Required Assessments	Before Step 1/Study Entry (*see footnote* ***a***)		Before Step 2/ randomization
Consent form signed by the patient (see Section 3.1.1)	X		
Central testing of ctDNA status (see Section 3.2.8)**f**			X
Determination of dMMR/MSI-H status (see 3.2.9)	X		
History & physical exam**b**	X	Within 28 days	
Assessment of concomitant medications**c**	X		
Performance status (Appendix A)**g**	X		
Height & weight	X		
CEA	X		
CBC/differential/platelet count**g**	X		
Total bilirubin/AST/ALT/Alkaline phosphatase**g**	X		
Serum chemistries: glucose, BUN**h**, sodium, potassium, chloride, bicarbonate or carbon dioxide, calcium, serum creatinine**g**	X		
Creatinine or creatinine clearance (calculated or measured)**g**	X		
Distant disease staging**d, g**	X	Within 45 days	
Pregnancy test**e, g**	X	Within 14 days	
Mandatory collection of whole blood for central testing of ctDNA status**f**			X
Optional collection of whole blood specimens**f**			X
Mandatory submission of archived resected primary tumor tissue for central testing of ctDNA status**f**			X
Mandatory submission of archived resected primary tumor tissue and uninvolved margin of resection (normal tissue)**f**			Within 60 days after randomization

a Informed consent must be obtained before performance of any screening assessments; however, results of screening tests or examinations performed as routine care before obtaining informed consent but within the timeframes outlined in Table 1 may be used rather than repeating required tests (cannot use ctDNA testing performed as routine care outside of the study for the required central ctDNA testing).

b Documentation of complete history and physical by a physician or other healthcare professional.

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

d For distant (metastatic) staging – It is recommended that the same imaging tests performed before study entry be used at follow-up time points. CT with IV contrast or MRI imaging is acceptable and **must** include chest, abdomen, and pelvis.

e For women of childbearing potential only. Pregnancy testing should be done according to institutional standards.

f Turn-around-time for ctDNA testing for patients at baseline (before randomization) is within 20 business days of receipt of the samples at Natera and turn-around-time for ctDNA testing for patients

at subsequent time points is within 10 business days of receipt of the sample at Natera. Turn-around-time starts once all samples are received for each timepoint. See Section 10.0 and the NRG-GI008 Pathology and Correlative Science Instructions. Mandatory and optional blood and tissue specimens cannot be collected until informed consent is obtained.

g These assessments must also be completed prior to re-randomization for Cohort A-Arm 2 patients who develop a ctDNA +ve assay during serial monitoring. Patient's willingness to be re-randomized must be affirmed. A Reaffirmation Form will be available on CTSU for patients to sign.

h For Canadian sites that collect serum urea instead of BUN, they may follow their local institutional guidelines for converting a urea test result to a BUN result.

Table 2. Tests, exams, and other requirements for all patients through Year 5 from randomization
Note: Arms 1, 3, and 4 patients should have treatment related assessments prior to each cycle and approximately 30 days after the last dose of therapy

Required assessments *(See footnote **a**)*	**Arm 2 ctDNA -ve patients[b]**	**Arm 1, Arm 3, and Arm 4 patients**		**All patients 9 months from randomization[b]**	**All patients 12 months from randomization through Year 5*[b]**
		Within 3 days before Day 1 of each cycle of chemotherapy *(beginning with Cycle 2)*	**30 days (+/-7 days) after the last dose of chemotherapy***		
History & physical exam[c]	X [(3 (+/- 2 weeks) and 6 months (+/- 4 weeks) from randomization)]	X	X		X [(every 6 months (+/- 4 weeks))]
Adverse event assessment[d]		X	X		
CBC/differential/platelet count		X	X		
Total bilirubin/ALT AST/Alk phos		X	X		
Serum chemistries: glucose, BUN[e],creatinine, sodium, chloride, bicarbonate, or carbon dioxide		X	X		
Potassium, magnesium, and calcium		X	X		
INR[f]		X	X		
CEA	X [(3 (+/- 2 weeks) and 6 months (+/- 4 weeks) from randomization)]	X (prior to week 13 and prior to last cycle of chemotherapy)		X	X [(every 6 months (+/- 4 weeks) AND at recurrence)]
Disease imaging[g]	X [(every 6 months (+/- 4 weeks) for all patients]				
Submission of unstained slides -optional[h]	X (for all patients at time of recurrence, second primary colorectal cancer, or second primary/secondary malignancy)				
Vital Status Update*[i]	X [(every 6 months (+/- 4 weeks) for all patients through Year 5*)]				

Table continued on next page

Table 2. Tests, exams, and other requirements for all patients through Year 5 from randomization(*continued*)

Required assessments	**Arm 2 patients ctDNA -ve patients[b]**	**Arm 1 patients**	**Arm 3 and 4 patients**
Whole Blood for ctDNA (mandatory)**[j]**	X (every 3 months (+/- 21 days) from randomization through Year 1 and then every 6 months (+/-28 days) through Years 2 and 3 from randomization or until imaging recurrence (+28 days) **[b]**	X (every 3 months (+/- 21 days) from randomization through Year 1 and then every 6 months (+/-28 days) through Years 2 and 3 from randomization or until imaging recurrence (+28 days)	X**[l]** (every 3 months (+/- 21 days) from randomization through Year 1 and then every 6 months (+/-28 days) through Years 2 and 3 from randomization or until imaging recurrence (+28 days)
Whole Blood (optional)**[i,k]**	X (every 3 months (+/- 21 days) from randomization through Year 1 and then every 6 months (+/-28 through Years 2 and 3 from randomization or until imaging recurrence (+28 days)**[b]**	X (3 and 6 months (+/-21 days) from randomization then every 6 months (+/-28 days) through Years 2 and 3 from randomization or until imaging recurrence (+28 days)	X**[l]** (3 and 6 months (+/- 21 days) from randomization then every 6 months (+/- 28days) through Years 2 and 3 or until imaging recurrence (+28 days)

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

b Patients who develop a ctDNA +ve assay during serial monitoring may transition to the ctDNA+ ve cohort (Cohort B) and undergo a second randomization to Arm 3 or Arm 4 treatment. See Section 3.1.3 and Section 3.4. Upon undergoing a second randomization, Table 2 assessments begin from the second randomization date.

c Updated history and physical with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up.

d See Section 7.0 for adverse events reporting requirements.

e For Canadian sites that collect serum urea instead of BUN, they may follow their local institutional guidelines for converting a urea test result to a BUN result.

f ***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 5.3.9).

g It is recommended that the same imaging tests performed before randomization be used at follow-up time points. See Section 12.0 for required confirmation of abnormal imaging related to study endpoints.

h Submission of unstained slides from tumor tissue obtained at the time of recurrence, second primary colorectal cancer, or second primary/secondary malignancy, if available, is only required for patients who have agreed to the ***optional tumor sample submission*** when signing the consent form (see Section 10.0 and the NRG-GI008 Pathology and Correlative Science Instructions).

i For patients who develop a ctDNA +ve assay during serial monitoring and are not willing to transition to the ctDNA+ve cohort (Cohort B), further therapy is at the investigator's discretion; however, patients will continue to be followed for disease recurrence, second primary colorectal cancer, or diagnosis of an invasive second primary/secondary malignancy and vital status until Year 5 from randomization.

j Submission of blood for ctDNA analysis is **required for all patients** (see Section 10.0 and the NRG-GI008 Pathology and Correlative Science Instructions).

k ***Requirement for all patients who agreed to optional blood collection and submission*** in the consent form *(*see Section 10.0 and the NRG-GI008 Pathology and Correlative Science Instructions).

l Assessments to be completed for Cohort A-Arm 2 patients who develop a ctDNA assay +ve during serial monitoring and are re-randomized to Cohort B.

*****Following documented disease recurrence, second primary colorectal cancer, or diagnosis of an invasive second primary/secondary malignancy, all protocol-specified tests, exams, assessments and specimen submissions will be discontinued. Patients will continue to be followed off treatment for vital status until Year 5 from randomization.

Note: If treatment with mFOLFOX6 must be discontinued for reasons other than disease recurrence, second primary colorectal cancer, or diagnosis of a second primary/secondary malignancy, all protocol-specified tests, exams, assessments and specimen submissions will continue (see Table 2 and Table 16). Patients will continue to be followed off treatment for vital status until Year 5 from randomization.

5.0 TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 **Treatment Regimens:** For patients on all arms, one cycle of chemotherapy (regimen per treating physicians' discretion – 5-FU or capecitabine with or without oxaliplatin) is allowed but not required after consent. The optional cycle of chemotherapy should be started ≥ 4 weeks from surgery and while awaiting Step 2 randomization. After randomization, refer to the appropriate regimen in Section 5. *Note: This optional cycle of chemotherapy is not to be included in the planned duration of the treatment regimen.*

5.1.1 Regimen for Cohort A-Arm 1 patients with ctDNA -ve

- Choice of regimen (mFOLFOX6 for 3-6 months or CAPOX for 3 months) is per the investigator (See Table 3 or Table 4).
- Chemotherapy should begin within 4 weeks following randomization and preferably no longer than 12 weeks from surgery.
- Central venous access is strongly recommended.
- Adverse events and results of laboratory safety assessments are to be reviewed prior to administration of study therapy.
- Drug administration order and infusion times for all chemotherapy in this protocol are per institutional guidelines.

Table 3. Treatment regimen for Cohort A -Arm 1 patients with ctDNA -ve (mFOLFOX6 for 3-6 months)

Drug	Dose	Administration	Dosing Interval	Planned Duration
Oxaliplatin	85 mg/m^2	IV, given concurrently through separate lines connected by Y-line tubing, over 2 hours. *(see footnote **a**)*	Day 1 every 2 weeks	6-12 cycles (12-24 weeks)
Leucovorin	400 mg/m^2			
5-Fluorouracil (5-FU)	400 mg/m^2	IV bolus recommended infusion time of 2–4 minutes immediately following oxaliplatin/leucovorin infusion		
	2400 mg/m^2	IV continuous infusion over 46-48 hours (total dose)		
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 C).				

Table 4. Treatment regimen for Cohort A -Arm 1 patients with ctDNA -ve (CAPOX for 3 months)

Drug	Dose	Administration	Dosing Interval	Planned Duration
Oxaliplatin	130 mg/m^2	IV given over 2 hours. *(see footnote **a**)*	Day 1 every 3 weeks	4 cycles (12 weeks)
Capecitabine	1000 mg/m^2 BID	By mouth *(see footnotes **b, c**)*	Days 1-14 every 3 weeks	

a Oxaliplatin is not compatible with normal saline solution. **b** Capecitabine should be taken in the morning and evening within 30 minutes after a meal (breakfast and dinner). Capecitabine dosing start may be +/- 1 day relative to the dose of oxaliplatin. Patients should be instructed not to cut or crush tablets. **c** Use of a patient pill diary (Appendix D) to record capecitabine compliance is recommended.

5.1.2 Regimen for Cohort A-Arm 2 patients with ctDNA-ve

- Monitor with serial ctDNA testing every 3 months (+/- 21 days) from randomization through Year 1 and then every 6 months (+/-28 days) through Years 2 and 3 from randomization until ctDNA+ve and/or recurrence).
- Patients who develop a ctDNA +ve assay during serial monitoring may transition to the ctDNA+ ve cohort (Cohort B) and undergo a second randomization to Arm 3 or Arm 4 treatment. See Section 3.1.3 and Section 3.4.
- Chemotherapy should begin within 4 weeks following re-randomization.
- For patients who develop a ctDNA +ve assay during serial monitoring and are not willing to transition to the ctDNA+ve cohort (Cohort B), further therapy is at the investigator's discretion. See Table 2 (footnote h) for follow up requirements.

5.1.3 Regimen for Cohort B-Arm 3 patients with ctDNA +ve

- mFOLFOX6 or CAPOX for 6 months (See Table 5 and 6).
- Chemotherapy should begin within 4 weeks following randomization and preferably no longer than 12 weeks from surgery.
- Central venous access is strongly recommended.
- Adverse events and results of laboratory safety assessments are to be reviewed prior to administration of study therapy.
- Drug administration order and infusion times for all chemotherapy in this protocol are per institutional guidelines.

Table 5. Treatment regimen for Cohort B -Arm 3 patients with ctDNA +ve (mFOLFOX6 for 6 months)

Drug	Dose	Administration	Dosing Interval	Planned Duration
Oxaliplatin	85 mg/m^2	IV, given concurrently through separate lines connected by Y-line tubing, over 2 hours. *(see footnote **a**)*	Day 1 every 2 weeks	12 cycles (24 weeks)
Leucovorin	400 mg/m^2			
5-Fluorouracil (5-FU)	400 mg/m^2	IV bolus recommended infusion time of 2–4 minutes immediately following oxaliplatin/leucovorin infusion		
	2400 mg/m^2	IV continuous infusion over 46-48 hours (total dose)		
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 C).				

Table 6. Treatment regimen for Cohort B- Arm 3 patients with ctDNA +ve (CAPOX for 6 months)

Drug	Dose	Administration	Dosing Interval	Planned Duration
Oxaliplatin	130 mg/m^2	IV given over 2 hours. *(see footnote **a**)*	Day 1 every 3 weeks	8 cycles (24 weeks)
Capecitabine	1000 mg/m^2 BID	By mouth *(see footnotes **b, c**)*	Days 1-14 every 3 weeks	

a Oxaliplatin is not compatible with normal saline solution.
b Capecitabine should be taken in the morning and evening within 30 minutes after a meal (breakfast and dinner). Capecitabine dosing start may be +/- 1 day relative to the dose of oxaliplatin. Patients should be instructed not to cut or crush tablets.
c Use of a patient pill diary (Appendix D) to record capecitabine compliance is recommended.

5.1.4 Regimen for Cohort B-Arm 4 patients with ctDNA+ve

- mFOLFIRINOX (5-FU, oxaliplatin, and irinotecan) for 6 months (See Table 7).
- Chemotherapy should begin within 4 weeks following randomization and preferably no longer than 12 weeks from surgery.
- Central venous access is strongly recommended.
- Adverse events and results of laboratory safety assessments are to be reviewed prior to administration of study therapy.
- Drug administration order and infusion times for all chemotherapy in this protocol are per institutional guidelines.

Table 7. Treatment regimen for Cohort B -Arm 4 patients with ctDNA +ve (mFOLFIRINOX for 6 months)

Drug	Dose	Administration	Dosing Interval	Planned Duration
Oxaliplatin	85 mg/m^2	IV, given concurrently through separate lines connected by Y-line tubing, over 2 hours. *(see footnote **a**)*	Day 1 every 2 weeks	12 cycles (24 weeks)
Leucovorin	400 mg/m^2			
Irinotecan	150 mg/m^2	IV continuous infusion over 30-90 minutes *(see footnote **b**)*		
5-Fluorouracil (5-FU)	2400 mg/m^2	IV continuous infusion over 46-48 hours (total dose)		

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 C).
b Prophylactic or therapeutic administration of intravenous or subcutaneous atropine 0.25 mg-1.0 mg should be considered (unless clinically contraindicated). Following completion of the first irinotecan infusion, patients should remain in the treatment area for a minimum of 1 hour in case acute abdominal cramping occurs.

5.2 Dose determinations

5.2.1 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.

5.2.2 Rounding Doses

Follow institutional practice for standard drug rounding. If Levoleucovorin is used, please refer to Appendix C for drug dose and administration instructions.

5.3 General Concomitant Medications and Supportive Care Guidelines

5.3.1 Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the treating physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

Herbal and Nutritional Supplement
The concomitant use of herbal therapies is generally not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, the use of general nutritional foundation supplements will be allowed including: calcium with vitamin D and/or minerals, Omega3s (fish oil), Vitamin B6, Vitamin B12, basic multivitamins , L-glutamine, or probiotics oral supplements will be permitted either at or below the recommended dosing by a healthcare provider. Herbal-based multivitamins are not allowed.

5.3.2 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**. See Section 6.0 for treatment modifications/management.
- 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. Biosimilars are also permitted based on institutional practice.
- Loratadine (10 mg) or similar agents are permitted if pegfilgrastim is used.

5.3.3 Management of diarrhea

Diarrhea is a commonly occurring toxicity with the therapies included in GI008. Without appropriate treatment, diarrhea can be prolonged, severe, and lead to dehydration and other complications. (See Appendix B for clinical management of diarrhea.)

- Inform patients that they may experience diarrhea while on chemotherapy and possibly for several weeks after chemotherapy has stopped.
- Patients **must** be instructed to:
  - have ready access to antidiarrheal agents (e.g., loperamide) starting on Day 1 of treatment.

- 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.
- continue prophylactic therapy as directed
- promptly report diarrhea symptoms
- 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.)

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.

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

5.3.4 Management of nausea or vomiting

Antiemetic therapy should be administered according to National Comprehensive Cancer Network (NCCN) (https://www.nccn.org) or American Society of Clinical Oncology (ASCO) clinical practice guidelines (Hesketh 2017). See Section 6.0 for dose modifications and delays.

5.3.5 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 10 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.

5.3.6 Irinotecan-related cholinergic syndrome (Cohort B-Arm 4)

- Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine, 0.25-1.0 mg IV or SC may be used to treat these symptoms or may be used prophylactically. Additional antidiarrheal measures may be used at the discretion of the investigator.
- Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal®) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).
- Diarrhea developing more than 24 hours after the irinotecan dose should be managed with loperamide as described in Section 5.3.3.

5.3.7 Management of anaphylaxis

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

5.3.8 Management of injection site reactions

Injection site reactions, including redness, swelling, and pain, have been reported with oxaliplatin. Extravasation, in some cases including soft tissue necrosis has occurred. For this reason, administration of oxaliplatin is recommended intravenously through a central venous catheter. Management of injection site reactions is per institutional guidelines.

5.3.9 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 that the 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.

5.3.10 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.
- **Targeted therapy**
  Administration of targeted therapy for malignancy is prohibited.
- **Radiation therapy**
  Administration of radiation therapy is prohibited.

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 for subsequent cancer events and for survival every 6 months until Year 3.

5.3.11 Participation in Other Trials

Patients are not permitted to participate in other therapeutic trials. However, trials that do not add experimental agents are allowed (e.g. imaging trials, quality of life, etc.). If a GI008 patient is considering participation in a supportive therapy trial, contact the NRG Oncology Clinical Coordinating Department.

5.4 Duration of Therapy

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

- Disease recurrence
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw consent for participation in the study

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance or refusal of therapy
- Pregnancy
  - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
  - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a female patient or the partner of a male patient participating in the study.
- Termination of the study by sponsor

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be reported in the Case Report Form.

6.0 TREATMENT MODIFICATIONS/MANAGEMENT

6.1 General instructions

- The CTCAE v5.0 must be used to grade the severity of AEs. Refer to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- Deviations from the recommended treatment modifications/management must be documented in the patient treatment record.
- In the event of disease recurrence, second primary colorectal cancer, or diagnosis of an invasive second primary/secondary malignancy, study therapy, protocol-specified tests, exams, assessments and specimen submissions will be discontinued; further therapy is at the investigator's discretion. Patients will continue to be followed off treatment for vital status until Year 5 from randomization.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., 5-FU, capecitabine, oxaliplatin, or irinotecan) and the dose of that component is held or modified in accordance with the guideline below, the other components may be administered per protocol guidelines.
- If several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- Any chemotherapy doses that have been reduced may not be escalated.
- **For any concomitant conditions apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate.** For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes only.
- Treatment schedule changes for non-medical reasons: When rescheduling chemotherapy for non-medical adjustments, refer to the memo "Scheduling Protocol Therapy for Non-medical Delays." 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 GI008/protocol related documents/supplemental. Any treatment schedule changes for non-medical reasons must be documented in the patient treatment record.

6.2 Treatment management for patients receiving mFOLFOX6

Chemotherapy dose modifications for patients are detailed in Tables 9 and 10. Dose modifications are based on the dose level changes outlined in Table 8. Additionally, the following mFOLFOX6 dose modification instructions must be followed:

- All dose modifications 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 Table 9 for dose modifications for the next cycle of mFOLFOX6.
- The leucovorin dose remains 400 mg/m^2 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 5-FU is discontinued, oxaliplatin treatment should continue per protocol unless otherwise contraindicated.
- If treatment with mFOLFOX6 must be discontinued for reasons other than disease recurrence, second primary colorectal cancer, or diagnosis of a second primary/secondary malignancy, all protocol-specified tests, exams, assessments and specimen submissions will continue (see Table 2 and Table 16). Patients will continue to be followed off treatment for vital status until Year 5 from randomization.

Table 8. 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 C).				

Table 9. Treatment management for mFOLFOX6 -(See Table 10 for oxaliplatin-specific toxicities.)

Important table instructions:

- All dose modifications for mFOLFOX6 are based on the dose level changes on Table 8.
- Dose modifications must be based on AEs that occurred during the cycle (column 2) ***and*** AEs present on the scheduled Day 1 of Cycles 2-12 (column 3). Refer to other applicable instructions in Section 6.1 and 6.2.
- Refer to footnote **a** 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 v5.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **b**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **c**)
Neutrophil count decreased: Grades 2 (ANC 1000-1199/mm^3)**d**	Maintain dose. *Consider use of growth factors to avoid delay with subsequent cycles.*	*Consider use of growth factors to avoid delay with subsequent cycles. Hold until ≥ 1200/mm^3. If recovery takes:* 1-3 wks – maintain dose
Grade 3, 4	Maintain dose or ↓ one dose level - at discretion of treating oncologist. *Consider use of growth factors to avoid delay with subsequent cycles.*	*Consider use of growth factors to avoid delay with subsequent cycles. Hold until ≥ 1200/mm^3. If recovery takes:* 1 wk – maintain dose or ↓ one dose level at discretion of treating oncologist; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2	Maintain dose	*Hold until ≥ 75,000/mm^3. If recovery takes:* 1-3 wks – maintain dose
Grade 3,4	Maintain dose or ↓ one dose level at discretion of treating oncologist	*Hold until ≥ 75,000/mm^3.If recovery takes:* 1-3 wks - ↓ one dose level
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

Table 9. Treatment management for mFOLFOX6 *(continued)*

CTCAE v5.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE **(**See footnote **b)**	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE **(**See footnote **c)**
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	*Consider use of growth factors to avoid delay with subsequent cycles.* Maintain dose *or* ↓ one dose level	*Consider use of growth factors to avoid delay with subsequent cycles.* 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
Other clinically significant AEs:[e] 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 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*.

b 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).

c 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 6.2 for instructions regarding further study treatment).

d For managing neutropenia in the setting of BEN, manage grade 2 neutropenia per institutional policy.

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

Table 10. Treatment management for oxaliplatin-specific toxicities

Nervous System Disorders		
Paresthesias/Dysesthesias/ Neuropathy (Peripheral motor; Peripheral sensory)	**1-7 day duration** *(intermittent or continuous)*	**> 7 day duration[a]** *(intermittent or continuous)*
Grade 1	Maintain dose	Maintain dose
Grade 2	Maintain dose[a]	Decrease ***oxaliplatin*** one dose level[b]
Grade 3	**First episode**: Decrease ***oxaliplatin*** one dose level **a** **Second episode**: Discontinue ***oxaliplatin***	Discontinue ***oxaliplatin***
Respiratory, thoracic and mediastinal disorders		
Laryngopharyngeal dysesthesia	**1-7 day duration** *(intermittent or continuous)*	**> 7 day duration** *(intermittent or continuous)*
Grade 1 Grade 2	Maintain dose and consider increasing infusion time of oxaliplatin to 6 hours	Maintain dose and consider increasing infusion time of oxaliplatin 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		
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 Hold until improved to ***less than moderate symptom intensity*** on the next treatment day.

b ***Hold oxaliplatin for persistent moderate intensity grade 2 neuropathy***. When improved to ***less than moderate intensity***, resume treatment with dose modification for oxaliplatin. If ***moderate intensity Grade 2 toxicity*** persists after 4 weeks of delay, discontinue oxaliplatin. Continue 5-FU + LV while oxaliplatin is held.

6.3 Treatment management for patients receiving CAPOX

Capecitabine dose modifications for patients treated with CAPOX are detailed in Table 12. See Table 10 for oxaliplatin-specific toxicities. Dose modifications are based on the dose level changes outlined in Table 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 capecitabine is held or discontinued, oxaliplatin continues per protocol unless otherwise contraindicated.
- Capecitabine and oxaliplatin doses that have been reduced may not be escalated.
- If a patient vomits after taking a capecitabine dose, the dose should be skipped and resumed upon the next scheduled administration. The patient should be instructed to notify the clinical team to have an antiemetic regimen adjusted and/or reason for vomiting addressed.
- If treatment with CAPOX must be discontinued for reasons other than disease recurrence, second primary colorectal cancer, or diagnosis of a second primary cancer or secondary malignancy, all protocol-specified tests, exams, assessments and specimen submissions will continue (see Table 2 and Table 16). Patients will continue to be followed off treatment for vital status until Year 5 from randomization.

Table 11. CAPOX 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	130	100	85	Discontinue
Capecitabine	1000 BID	750 BID	500 BID	Discontinue

Table 12. Treatment management for CAPOX (See Table 10 for oxaliplatin-specific toxicities.)

Important table instructions: • Dose modifications for capecitabine are based on the dose level changes on Table 11. • **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 v5.0 Adverse Event/Grade	Modifications for AEs that REQUIRED DELAY IN TREATMENT
Neutrophil count decreased: Grades 2 (ANC 1000-1199/mm^3), 3, 4**a**	*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

Table 12. Treatment management for capecitabine *(continued)*

CTCAE v5.0 Adverse Event/Grade	Modifications for AEs that REQUIRED DELAY IN TREATMENT
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
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
a For managing neutropenia in the setting of BEN, manage grade 2 neutropenia per institutional policy. ***** Determination of "clinically significant" AEs is at the discretion of the investigator.	

6.4 Treatment management for patients receiving mFOLFIRINOX

mFOLFIRINOX dose modifications for patients treated with mFOLFIRINOX are detailed in Table 14. Dose modifications are based on the dose level changes outlined in Table 13.

Additionally, the following dose modification instructions must be followed:

- All dose modifications 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 Table 14 for dose modifications for the next cycle of mFOLFIRINOX.
- The leucovorin dose remains 400 mg/m^2 regardless of changes in the 5-FU, oxaliplatin, and irinotecan doses. If 5-FU is held, leucovorin should also be held.
- If oxaliplatin is discontinued, treatment should continue with 5-FU, leucovorin, and irinotecan.
- If irinotecan is discontinued, treatment should continue with 5-FU, leucovorin, and oxaliplatin.
- If 5-FU and leucovorin are discontinued, treatment should continue with irinotecan and oxaliplatin.
- If treatment with mFOLFIRINOX must be discontinued for reasons other than disease recurrence, second primary colorectal cancer, or diagnosis of a second primary/secondary malignancy, all protocol-specified tests, exams, assessments and specimen submissions will continue (see Table 2 and Table 16). Patients will continue to be followed off treatment for vital status until Year 5 from randomization.

Table 13. Dose levels for mFOLFIRINOX

	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 infusion	2400	1920	1600	Discontinue
Irinotecan	150	135	120	Discontinue
*Levoleucovorin at 200 mg/m^2 can be substituted for leucovorin per institutional practice or as needed for drug availability (see Appendix C).				

Table 14. Treatment management for mFOLFIRINOX -(See Table 10 for oxaliplatin-specific toxicities.)

Important table instructions:

- All dose modifications for mFOLFIRINOX are based on the dose level changes on Table 13.
- Dose modifications must be based on AEs that occurred during the cycle (column 2) ***and*** AEs present on the scheduled Day 1 of Cycles 2-12 (column 3). Refer to other applicable instructions in Section 6.1 and 6.4.
- Refer to footnote **a** for management of anemia.
- Modifications in dose levels apply to 5-fluorouracil, irinotecan, and oxaliplatin unless otherwise indicated; leucovorin doses remain unchanged.
- Dose modifications must be based on the AE requiring the greatest modification.

CTCAE v5.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **b**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **c**)
Neutrophil count decreased: Grades 2 (ANC 1000-1199/mm^3)	Maintain dose *Consider use of growth factors to avoid delay with subsequent cycles.*	*Consider use of growth factors to avoid delay with subsequent cycles.* *Hold until ≥ 1200/mm^3. If recovery takes:* 1-3 wks – maintain dose *or* ↓ one dose level at discretion of treating oncologist**d**
Grade 3, 4	Maintain dose *or* ↓ one dose level - at discretion of treating oncologist *Consider use of growth factors to avoid delay with subsequent cycles.*	*Consider use of growth factors to avoid delay with subsequent cycles.* *Hold until ≥ 1200/mm^3. If recovery takes:* 1 wk – maintain dose *or* ↓ one dose level at discretion of treating oncologist; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2	Maintain dose	*Hold until ≥ 75,000/mm^3.* *If recovery takes:* 1-3 wks – maintain dose
Grade 3,4	Maintain dose *or* ↓ one dose level at discretion of treating oncologist	*Hold until ≥ 75,000/mm^3.If recovery takes:* 1-3 wks - ↓ one dose level
GI: **Diarrhea** *(despite optimal antidiarrheal management)* Grade 2	Maintain dose**e**	↓ 5-FU *and* irinotecan one dose level
Grade 3	↓ 5-FU *and* irinotecan one dose level	↓ 5-FU *and* irinotecan one dose level
Grade 4	↓ 5-FU, irinotecan *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* ↓ irinotecan *and* oxaliplatin one dose level
Grade 4	↓ 5-FU two dose levels *and* ↓ irinotecan *and* oxaliplatin one dose level	Discontinue

Table 14. Treatment management for mFOLFIRINOX *(continued)*

CTCAE v5.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **b**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **c**)
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 and irinotecan one dose level	*Hold until bilirubin returns to the* ***baseline grade*** *and AST and alk phos have returned to ≤ grade 1, then:* ↓ oxaliplatin *and* irinotecan one dose level
Grade 3	↓ one dose level	*Hold until bilirubin returns to the* ***baseline grade*** *and AST and alk phos have returned to ≤ grade 1, then:* ↓ two dose levels *or* discontinue
Grade 4	Discontinue	Discontinue
Febrile neutropenia: Grade 3	*Consider use of growth factors to avoid delay with subsequent cycles.* Maintain dose *or* ↓ one dose level	*Consider use of growth factors to avoid delay with subsequent cycles.* 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
Other clinically significant AEs:[f] 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 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.*

b 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).

c 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 mFOLFIRINOX (see Section 6.4 for instructions regarding further study treatment).

d For managing neutropenia in the setting of BEN, manage grade 2 neutropenia per institutional policy.

e If multiple episodes of grade 2 diarrhea occur during the cycle but do not delay the subsequent cycle, irinotecan may be decreased one dose level at the discretion of the investigator.

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

Table 14. Treatment management for mFOLFIRINOX (*continued*)

Nervous System Disorders		
Paresthesias/Dysesthesias/ Neuropathy (Peripheral motor; Peripheral sensory)	**1-7 day duration** *(intermittent or continuous)*	**> 7 day duration** *(intermittent or continuous)*
Grade 1	Maintain dose	Maintain dose
Grade 2	Maintain dose[a]	Decrease ***oxaliplatin*** one dose level[b]
Grade 3	**First episode**: Decrease ***oxaliplatin*** one dose level[a] **Second episode**: Discontinue ***oxaliplatin***	Discontinue ***oxaliplatin***
Grade 4	Discontinue	
Respiratory, thoracic and mediastinal disorders		
Laryngopharyngeal dysesthesia	**1-7 day duration** *(intermittent or continuous)*	**> 7 day duration** *(intermittent or continuous)*
Grade 1 Grade 2	Maintain dose and consider increasing infusion time of oxaliplatin to 6 hours	Maintain dose and consider increasing infusion time of oxaliplatin 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		
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 Hold until improved to ***less than moderate symptom intensity*** on the next treatment day.

b ***Hold oxaliplatin for persistent moderate intensity grade 2 neuropathy***. When improved to ***less than moderate intensity***, resume treatment with dose modification for oxaliplatin. If ***moderate intensity Grade 2 toxicity*** persists after 4 weeks of delay, discontinue oxaliplatin. Continue 5-FU + LV and irinotecan while oxaliplatin is held.

6.5 Management for Arm 2 patients with ctDNA -ve

Arm 2 patients will be monitored with serial ctDNA testing every 3 months (+/- 21 days) from randomization through Year 1 and then every 6 months through Years 2 and 3 from randomization until ctDNA+ve and/or recurrence). Patients who develop a ctDNA +ve assay during serial monitoring will transition to the ctDNA+ ve cohort (Cohort B) and undergo a second randomization to Arm 3 or Arm 4 treatment. See Section 3.1.3 and Section 3.4. For patients who develop a ctDNA +ve assay during serial monitoring and are not willing to transition to the ctDNA+ve cohort (Cohort B), further therapy is at the investigator's discretion. See Table 2 for follow up requirements.

7.0 ADVERSE EVENT REPORTING REQUIREMENTS

7.1 Study Agents

7.1.1 Investigational agents

There are no investigational agents in NRG-GI008.

7.1.2 Commercial agents

The commercial agents in NRG-GI008 are 5-fluorouracil (NSC #19893), leucovorin (NSC #3590), levoleucovorin (NSC-#807037), oxaliplatin (NSC #266046), capecitabine (NSC #712807), and irinotecan (NSC #61648).

7.2 Adverse Events and Serious Adverse Events

7.2.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. 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 website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7.2.2 Definition of an Adverse Event (AE)

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 (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of study treatment including radiation therapy, surgery, device, and drug.

7.3 Adverse Events for Commercial Agents

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

7.4 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in Table 15 will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via RAVE-CTEP-AERS Integration.

Refer to Section 13.4 for important operational details/information about RAVE-CTEP-AERS Integration and how to obtain the Expedited Safety Reporting Rules Evaluation User Guide.

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation-therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology Statistics and Data Management Center by telephone at 412-624-2666. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

For expedited reporting questions contact: saereportingpgh@nrgoncology.org

7.4.1 Expedited Reporting Methods

- **CTEP-AERS 24-Hour Notification** requires that a CTEP-AERS 24-hour notification is electronically submitted **within 24 hours** of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a by a complete report within **5 calendar days.**
- **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 15).
- CTEP-AERS documentation should be uploaded via the CTSU Source Documentation Portal (SDP). Documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. Remove all patient names and identifiers such as social security number, address, telephone number, etc., from the documents.
- A serious adverse event that meets expedited reporting criteria as outlined in the AE Reporting Table but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the "NOT recommended" assessment. The CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.4.2 Expedited Reporting Requirements

Expedited reporting requirements begin with the first dose of post-randomization chemotherapy. Expedited reporting requirements for all patients are provided in Table 15.

Adverse events that are unequivocally due to disease recurrence or second primary cancer should not be reported as SAEs.

Table 15. Expedited reporting requirements for adverse events that occur within 30 days of the last dose of post-randomization chemotherapy[1]

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

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the study therapy (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 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	Not required		10 Calendar Days	24-Hour, 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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.

1Serious adverse events that occur more than 30 days after the last dose of post-randomization chemotherapy 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 day reports for:

- Grade 3 adverse events

Effective Date: May 5, 2011

7.4.3 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.

7.4.4 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.

7.4.5 Secondary Malignancy

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

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE to be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. 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 GI008 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 one 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 GI008 Follow-up Folder in Medidata Rave.

7.4.7 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via CTEP-AERS. In addition, the Pregnancy Information Form included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90

days after the last dose of study therapy must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

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 13.2).
- **All ≥ grade 2 adverse events** that occurred during post-randomization study therapy must be reported on the GI008 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 GI008 Adverse Event forms through Medidata Rave must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology Statistics and Data Management Center is required, remove patient names and identifiers such as social security number, address, telephone number, etc., from reports and supporting documentation.
- AEs following a documented colon cancer recurrence or second primary cancer should not be reported.

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 GI008 Adverse Event and Treatment forms according to the following schedule:

Arm 1 (mFOLFOX6 for 3-6 months or CAPOX for 3 months) and **Arm 3 (**mFOLFOX6 or CAPOX for 6 months)

- At the end of each cycle and 30 (+/-7) days after the last dose of chemotherapy.

Arm 4 (mFOLFIRINOX for 6 months)

- At the end of each cycle and 30 (+/-7) days after the last dose of chemotherapy.

7.6 Reporting Colon Cancer Recurrence and Second Primary Cancer

Report colon cancer recurrence, second primary colorectal cancer, and second primary cancer (a malignancy which is unrelated to the treatment of a prior malignancy and which is not a metastasis from the initial malignancy) within the GI008 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 here. (See Section 7.4.4 for reporting instructions for ***secondary*** malignancies.)

8.0 REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

8.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials 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). Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- 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)	✓	✓	✓		

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;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

8.2.1 IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (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. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. 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 (SSW) for Local Context 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 email 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 for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an Active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval and on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

8.2.2 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);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

8.2.3 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 to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org)
- Click on *Protocols* in the upper left of the 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-GI008);
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

8.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

8.2.5 Checking Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to by Protocol, Registration Status, Protocol Status, and/or IRB type.

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

8.3 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, informed consent is obtained, and the study site is listed as 'approved' in the CTSU RSS.
Patients must have signed and dated all applicable consents and authorization forms.

8.3.1 Oncology Patient Enrollment Network (OPEN)

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 LPOs registration/randomization systems or the 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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or to request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the 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 Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may 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 Reimbursement

To receive site reimbursement for biospecimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Refer to the protocol-specific funding page on the CTSU members' website for additional information (Protocol NRG-GI008 > Funding Information.). Timely entry of completion dates is recommended as this will trigger site reimbursement.

8.5 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 cannot be tolerated 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 colon cancer becomes available.

If study therapy is stopped, study data, other materials, and the blood and tumor samples should be submitted according to the study schedule unless the patient withdraws from the study (see Section 8.7).

8.6 Patient-Initiated Discontinuation of Study Therapy

Even after a patient agrees to take part in this study, the patient 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, other materials, and the blood and tumor samples should be submitted according to the study schedule.

8.7 Patient-Initiated Consent 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), the study applicable form should be completed in Medidata Rave to report the patient's consent withdrawal.

NOTE: This should not be done if the patient has only chosen to stop protocol treatment and is willing to still be followed. (See Section 5.4).

9.0 DRUG INFORMATION

Oxaliplatin, 5-fluorouracil, leucovorin, irinotecan, and capecitabine are obtained by the investigator from commercial supply.

9.1 Oxaliplatin (NSC #266046)

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.1.1 Adverse Events

Refer to the oxaliplatin package insert.

9.1.2 Availability/Supply

Please see Section 5.1 for administration instructions. Refer to the current FDA-approved package inserts provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.2 5-fluorouracil (NSC #19893)

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.2.1 Adverse Events

Refer to the 5-fluorouracil package insert.

9.2.2 Availability/Supply

Please see Section 5.1 for administration instructions. Refer to the current FDA-approved package inserts provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.3 Leucovorin (NSC #3590)

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.3.1 Adverse Events

Refer to the leucovorin package insert.

9.3.2 Availability/Supply

Please see Section 5.1 for administration instructions. Refer to the current FDA-approved package inserts provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.4 **Irinotecan (NSC #616348)**

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.4.1 Adverse Events

Refer to the irinotecan package insert.

9.4.2 Availability/Supply

Please see Section 5.1 for administration instructions. Refer to the current FDA-approved package inserts provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation.

9.5 **Levoleucovorin (NSC #807037)**

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.5.1 Adverse Events

Refer to the levoleucovorin package insert.

9.5.2 Availability/Supply

Please see Section 5.1 for administration instructions. Refer to the current FDA-approved package inserts provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.6 **Capecitabine (NSC #712807)**

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.6.1 Adverse Events

Refer to the capecitabine package insert.

9.6.2 Availability/Supply

Please see Section 5.1 for administration instructions. Refer to the current FDA-approved package inserts provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

10.0 PATHOLOGY/BIOSPECIMEN

10.1 Overview of Tumor and Blood Specimen Submissions

Submission of whole blood for ctDNA analysis, archived resected primary tumor tissue (FFPE), and uninvolved margin of resection (normal tissue) (FFPE) is required for all patients who consent to enrollment in NRG-GI008. ***Submission of optional tumor tissue and blood specimens is only required for patients who agree to submission of optional tumor tissue and blood in the GI008 consent form.*** Tumor and blood samples for all patients will be collected at the specified timepoints outlined in Table 16.

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

See detailed specimen collection/processing/shipping instructions in the NRG-GI008 Pathology and Correlative Science Instructions.

This study will include collection of biospecimens for future analyses. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

Table 16. Mandatory and optional sample requirements

Specimen Type	Collection Time Points	Shipping
Archived resected primary tumor tissue (FFPE) (mandatory)**a,b,c**	**All patients** Baseline (before randomization)**a,b,c**	Natera 13011 McCallen Pass Building A, Suite 100 Austin, TX 78753
Whole blood ctDNA (two (2) 10 mL Streck cell-free BCT tubes-mandatory)**b,c,d**	**All patients b,c,d** Baseline (before randomization) **Arm 1 patients** • Every 3 months (+/- 21 days) from randomization through Year 1 and then every 6 months (+/-28 days) through Years 2 and 3 from randomization (3, 6, 9, 12, 18, 24, 30, and 36 months) or until imaging recurrence (+28 days) **Arm 2 ctDNA -ve patients** • Every 3 months (+/- 21 days) from randomization through Year 1 and then every 6 months (+/-28 days) through Years 2 and 3 from randomization (3, 6, 9,12, 18, 24, 30, and 36 months) or until imaging recurrence (+28 days) **Arm 3 and 4 patients** • Every 3 months (+/- 21 days) from randomization through Year 1 and then every 6 months (+/-28 days) through Years 2 and 3 from randomization (3, 6, 9, 12, 18, 24, 30, and 36 months) or until imaging recurrence (+28 days)	
Whole blood (one (1) 6 mL purple top tube (EDTA) mandatory)**b,c,d**	**All patients** Baseline (before randomization)**b,c,d**	
Archived resected primary tumor tissue and uninvolved margin of resection (normal tissue) (FFPE) (mandatory)**b,e**	**All patients** Must be submitted within 60 days after randomization	NRG Oncology Biospecimen Bank - Pittsburgh 1307 Federal Street, Suite 303 Pittsburgh, PA 15212 Phone: 412-697-6611 E-mail: nrgbiobankpgh@nrgoncology.org
Unstained slides at time of recurrence/secondary malignancy (optional)**f**	**All patients** • At recurrence or second primary/secondary malignancy	

Table continued on next page

Table 16. Mandatory and optional sample requirements (*continued)*

Whole blood (five (5) 10 mL purple top tubes (EDTA) before randomization and collect two (2) 10 mL purple top tubes (EDTA), at each of the other time points (optional)**b,g**	**All patients** • Baseline (before randomization)**g** **Arm 1 patients** • 3 and 6 months (+/-21 days) from randomization then every 6 months (+/-28 days) through Years 2 and 3 from randomization (3, 6, 12, 18, 24, 30, and 36 months) or • until imaging recurrence (+28 days) **Arm 2 ctDNA -ve patients** • Every 3 months (+/- 21 days) from randomization through Year 1 and then every 6 months (+/-28 days) through Years 2 and 3 from randomization (3, 6, 9, 12, 18, 24, 30, and 36 months) or • until imaging recurrence (+28 days) **Arm 3 and 4 patients** • 3 and 6 months (+/- 21 days) from randomization then every 6 months (+/-28 days) through Years 2 and 3 from randomization (3, 6, 12, 18, 24, 30, and 36 months) or • until imaging recurrence (+28 days)	Baylor College of Medicine NRG Oncology Serum Bank Room N330C One Baylor Plaza Houston, TX 77030

a Submit an archived paraffin block (FFPE) from **resected primary tumor tissue** to Natera. Please refer to the NRG-GI008 Pathology and Correlative Science Instructions for the tumor tissue requirements.

b First priority for submission of samples if there is limited tumor tissue and whole blood available is to submit to Natera.

c Patients who otherwise meet eligibility criteria and have had ctDNA status checked with the Signatera™ assay as routine care outside of the study, will require the submission of an archived paraffin block (FFPE) from resected primary tumor tissue, the baseline mandatory whole blood (Streck) specimen, and the whole blood (EDTA) sent to Natera for the ctDNA testing.

d Collect two (2) 10mL Streck cell-free BCT tubes and one (1) 6 mL purple top tube (EDTA) before randomization and then collect two (2)-10mL Streck cell-free BCT tubes at all of the other time points during a routine phlebotomy procedure for other standard labs. All mandatory specimens should be collected in their entirety prior to collection of any optional sample collection. Mandatory blood specimen at baseline cannot be collected until informed consent is obtained.

e Submit an archived paraffin block (FFPE) from **resected primary tumor tissue** and submit an archived paraffin block (FFPE) from **an uninvolved margin of resection (normal tissue)** to NRG Oncology Biospecimen Bank, if tissue is available after submission of tissue to Natera.

f If a biopsy was done anytime through Year 3 from randomization as part of routine care at the time of disease recurrence, second primary colorectal cancer, or diagnosis of a second primary cancer or secondary malignancy, submission of one H & E slide with an additional ≥ 15 unstained slides is required for patients who have agreed to the **optional** biobanking portion of this study.

g For patients participating in the optional specimen collection, collect five (5) 10 mL purple top tubes (EDTA) before randomization and collect two (2) 10 mL purple top tubes (EDTA), at each of the other time points during a routine phlebotomy procedure for other standard labs. *Note:* Optional blood specimen at baseline cannot be collected until informed consent is obtained and cannot be shipped until after randomization.

Note: Refer to the NRG-GI008 Pathology and Correlative Science Instructions for tumor and blood sample collection, alternative sample submission, processing, and submission instructions.

10.2 Specimen Submission Information

Refer to the GI008 Pathology, Correlative Science, and Imaging Submission Instructions in the Members' Area of the CTSU website for details regarding submission of specimens.

- If there is insufficient material available for the mandatory specimen submissions as outlined on Table 16, the prioritization for specimen submissions is to Natera for ctDNA testing.

10.3 Integral Marker Testing

10.3.1 ctDNA testing

The Signatera Test, offered by Natera Inc., is a personalized multiplex-PCR, and next-generation sequencing (NGS) based in-vitro diagnostic test targeting tumor-specific mutations. It is intended for the detection of circulating tumor DNA (ctDNA) isolated from anticoagulated peripheral whole blood from post-surgical patients diagnosed with localized or advanced solid tumors. The Signatera Test will be run as a centralized laboratory developed test that is developed and validated under Design Controls. The test will be run in a CLIA-certified, CAP-accredited laboratory located at the Natera facility in the United States. The CAP/CLIA accreditation ensures that the lab meets the federal regulations for clinical diagnostic testing, ensuring quality and safety in the laboratory and test results.

10.3.2 Method of testing

The Signatera Test first identifies variants associated with the patient's tumor and then tracks these variants in cell-free DNA (cfDNA) isolated from plasma at subsequent blood draws over time. The test includes four primary processes:

1) Whole exome sequencing of formalin-fixed paraffin-embedded (archival) tumor DNA and matched normal DNA from whole blood.

2) Bioinformatic processing of the Whole exome sequencing (WES) results to select clonal variants of the tumor DNA

3) Multiplex PCR (mPCR) library and NGS analysis of cfDNA samples isolated from plasma

4) Bioinformatic processing of the cfDNA NGS data for the detection and quantification of ctDNA

Processes 1 and 2, referred to as the WES Pipeline, are only performed once for each patient to identify clonal tumor-specific, somatic, single nucleotide variants (SNVs) (not genes). Processes 3 and 4, referred to as the Plasma Pipeline, are performed multiple times with recurring blood tests to monitor patient's ctDNA level over time.

The Signatera Test has been analytically validated for its use within the context of the clinical study and meets the requirements for reproducibility, precision, accuracy, robustness, and limit of detection.

The Signatera Test reports presence or absence of tumor DNA. A patient's plasma sample is considered ctDNA+ve when at least two of sixteen SNV targets are above the confidence threshold. Otherwise, a negative result is issued. This test is not designed to detect or report germline variations, nor to infer hereditary cancer risk for the patient.

10.3.3 Reporting and Location of Testing

Results of ctDNA testing from study entry for all patients will be provided to the investigator. For Group 2 patients, investigators will be provided results for patients who develop ctDNA +ve assay during serial monitoring to provide opportunity for re-randomization into Groups 3 or 4.

Natera
13011 McCallen Pass
Building A, Suite 100
Austin, TX 78753

10.4 **Exploratory Analyses**

The tumor samples and blood collected in this study will be used for studies specified in the GI008 protocol and for studies to be conducted in the future related to the purposes of the GI008 study and not currently described in the protocol document.

For the collected tumor and blood specimens, the specific aims are:

While genomic analysis is required of the tumor from the surgically resected specimens to verify the ctDNA integral biomarker, remaining FFPE tumor tissue collected will be stored for future post-hoc analyses of supplemental biomarkers that can further refine or expand the role of this evolving field. Additional serial blood collection, in parallel with the times of ctDNA collections and at the time of any relapse, will be performed. Importantly, these liquid biospecimens will be prepared with plans for future analyses of circulating biomarkers that may further refine prognosis and prediction of treatment response. These may include temporal kinetics and quantification of ctDNA but also other emerging technologies including but not limited to ctRNA, proteomics and CTC assessments, as examples.

11.0 **SPECIAL STUDIES (NON-TISSUE)-NON APPLICABLE**

12.0 DIAGNOSIS OF COLON CANCER RECURRENCE

The diagnosis of a first colon cancer recurrence should be made only when the clinical and laboratory findings meet the criteria of "acceptable" as defined below. Any recurrence of malignant disease should be proven by biopsy whenever possible.

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

Supporting documentation must be submitted with the GI008 Follow-up folder in Medidata Rave following diagnosis of colon cancer recurrence or invasive second cancer. The documentation will be reviewed at the NRG Oncology SDMC to determine the method(s) used to document the recurrence, the anastomotic location(s) of the recurrence, and the type of second cancer.

12.1 Abdominal and/or pelvic sites

12.1.1 Anastomotic

Acceptable: positive cytology or biopsy

12.1.2 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.

12.1.3 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.

12.1.4 Ascites

Acceptable: positive cytology

12.1.5 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 colon cancer 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 colon cancer 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.

12.1.6 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.

12.1.7 Abdominal wall, perineum, and scar

Acceptable: positive cytology or biopsy

12.2 **Non-abdominal and non-pelvic sites**

12.2.1 Skeletal

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

12.2.2 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.

12.2.3 Bone marrow

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

12.2.4 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).

12.3 **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.

12.4 **Second primary cancer**

Second primary cancer is defined any ***invasive*** 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.

12.5 **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.

13.0 DATA AND RECORDS

13.1 Data Management/Collection

Medidata Rave is the 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.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (Lab Admin), Rave SLA or Rave Investigator.
- Rave role requirements:
    - Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate plus (AP) registration type;
    - Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
    - Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/InvestigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in the Regulatory application, 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 either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. 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 eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen 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 replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management 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 or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

13.2 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 more timely monitoring of patient safety and care. See Section 7.4 and Section 7.5 for information about expedited and routine reporting.

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

13.3 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, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.4 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave**.

Treatment-emergent AEs: All AEs that occur after start of post-randomization treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered

in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence, that Internet connectivity is lost; a 24-hour notification is to be made to the NRG Oncology Statistics and Data Management Center by telephone at 412-624-2666. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents>Adverse Event Reporting* ; and
- *Additional Resources > CTSU Operations Information > User Guides & Help Topics.*

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

13.5 Global Reporting/Monitoring

***Demography** monitoring:*

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design Overview

This study contains two cohorts, the ctDNA negative cohort (-ve, Cohort A) and the ctDNA positive cohort (+ve, Cohort B) based on the post-operation ctDNA test results. A randomized phase II/III study will be conducted within each cohort.

Cohort A (ctDNA -ve): patients will be randomized into immediate treatment arm (**Arm 1**) and delayed (based on serial ctDNA surveillance) treatment arm (**Arm 2**). The primary endpoint for phase II of Cohort A is time to ctDNA (+ve) status (TTPos) and the primary endpoint for phase III of Cohort A is disease-free survival (DFS). Patients on Arm 2 who turned ctDNA (+ve) will cross over to Cohort B study.

Cohort B (ctDNA +ve): patients will be randomized to receive either FP (5-FU/ capecitabine + oxaliplatin, **Arm 3**) or FOLFIRINOX (5-FU + oxaliplatin + irinotecan, **Arm 4**) for 6 months. The primary endpoint for both phase II and III of Cohort B is DFS.

Synchronized accrual hiatus: there will be an accrual hiatus about 12-14 months between phase II and phase III portion of the trial in both Cohorts to allow obtaining the phase II results. The hiatus of the two cohorts will largely overlap. If the phase II result of Cohort B turns out to be negative, we will stop the crossover of Cohort A Arm 2 patients to Cohort B.

14.2 Primary Aims and Endpoints

14.2.1 Cohort A (ctDNA-ve) Phase II

Aim: To compare the time to ctDNA (+ve) status between immediate adjuvant chemotherapy and delayed adjuvant chemotherapy in stage III colon cancer patients who were ctDNA (-ve) post-surgery.

Endpoint: TTPos is defined as time from randomization until ctDNA (+ve) positive event: TTPos events are first ctDNA positive result after randomization for the immediate adjuvant chemo arm (Arm 1), 2nd ctDNA positive result after randomization for the delayed adjuvant chemo (Arm 2, to allow for the potential effect of delayed adjuvant chemotherapy) and recurrence without a positive ctDNA result for both arms. Patients without any post-randomization positive results and recurrence will be censored at the last ctDNA test for both arms. Patients with only 1 positive results in Arm 2 will be censored at the last ctDNA test (either positive or negative). The following table tabulated all possible scenarios on the coding of TTPos endpoint.

Table 17. TTPos Endpoint Code

Arm 1=Immediate adjuvant 2=Delayed adjuvant	First ctDNA positivity	Impact of delayed adjuvant	Second ctDNA positive	Time-to-ctDNA +ve event Outcome
1	Positive	N/A	Any	Event at time of First positive
1	None and no recurrence	N/A	N/A	Censor at last ctDNA test
2	Positive	Cleared on the test after first positive	Positive	Event at time of Second positive

2	Positive	Cleared on the test after first positive	No second positive	Censor at last ctDNA test
2	Positive	No clearance on the test after first positive, two positive tests in a row	Any	Event at time of First positive
2	Positive	No test after first positive		Censored at the time of First positive
2	None or Lost to follow up before turning positive, No recurrence	N/A	N/A	Censor at last ctDNA test
1 and 2	Recurrence before any post-randomization positive	N/A	N/A	Event at time of recurrence

14.2.2 Cohort A (ctDNA-ve) Phase III

Aim: To compare the time to DFS event between immediate adjuvant chemotherapy and delayed adjuvant chemotherapy in stage III colon cancer patients who were ctDNA (-ve) post-surgery.

Endpoint: DFS is defined as time from randomization to recurrence, second primary colorectal cancer or death from any cause.

14.2.3 Cohort B (ctDNA+ve) Phase II/III

Aim: To compare the time to DFS event between two Arm 3 (5-FU (or capecitabine) +oxaliplatin and Arm 4 (5-FU+oxaliplatin and irinotecan) in colon cancer patients who were ctDNA(+ve) post-surgery.

Endpoint: DFS is defined as time from randomization to recurrence, second primary colorectal cancer or death from any cause.

14.3 **Secondary Objectives and Endpoints (Both Cohorts)**

- To estimate the incidence (presence) of ctDNA in blood following resection of stage III colon cancer. This endpoint will be reported along with the phase II results of the two cohorts.
- To determine the overall survival (OS), defined as time from randomization to death of any cause, according to cohort and treatment.
- To determine the time to recurrence (TTR), defined as time from randomization to disease recurrence, according to cohort and treatment. Censoring will be at last patient contact or death.
- To assess the compliance of adjuvant chemotherapy in each arm.

14.4 Exploratory Objectives and Endpoints

- To explore ctDNA kinetics post-surgical resection of stage III colon cancer and its association with prognosis.
- To characterize genomic profiles and its association with TTR using a ctDNA assay in patients with resected colon cancer.

14.5 Stratification and randomization

Randomization ratio for both cohorts will be 1:1. The stratification factors for Cohort A include disease stage (II/IIIA vs IIIB vs/IIIC) and intended FP chemotherapy (5-FU vs Capecitabine). The stratifications factors for Cohort B include intended FP chemotherapy (5-FU vs Capecitabine) and the initial post-op ctDNA status (+ve vs. -ve). An adaptive randomization scheme that avoids imbalance within each strata will be employed. We use an algorithm based on the method described by White and Freedman (White 1978) that incorporates Efron's (Efron 1971) biased coin approach. Our algorithm computes a score for each treatment arm as the weighted sum of the number of patients on that treatment arm. When the treatment scores differ by less than a pre-defined tolerance, patients are randomly assigned treatment in an unbiased fashion (treatment equally likely). When the treatment scores differ by more than a pre-defined tolerance, patients are randomly assigned treatment using a biased-coin approach where the bias depends on the difference in scores.

14.6 Patient population used for analysis

14.6.1 Intent-to-treat population

The intent-to-treat (ITT) population include all patients randomized. ITT will be used for analysis of primary and secondary endpoints except for toxicity. Patients will be analyzed according to their randomly assigned arm regardless of treatment actually received.

14.6.2 Safety population

The safety population includes all patients who receive at least one dose of study therapy and will be used for toxicity endpoint.

14.7 Power Justification Expected Sample Size and Accrual Estimates

Phase II:

In phase II of the trial, we aim to enroll 1000 eligible patients post-operatively for ctDNA analyses. We estimate 70% or 700 patients will be ctDNA (-ve) who will be randomized (1:1) to immediate vs delayed (based on serial ctDNA surveillance) adjuvant chemotherapy. The primary endpoint of this cohort is to evaluate time to ctDNA positivity utilizing a non-inferiority design. Assuming a null hypothesis of inferiority, H0: 88% free of ctDNA positivity at 1 year for mFOLFOX6, 78.5% delayed (HR=1.9); and an alternative hypothesis of a small detriment with delayed chemo HA 88 vs 85.7% free of ctDNA positivity at 1 year (HR=1.21)). One hundred seventy-three events provide 90.7% power (chance to reject H0), assuming HA is true, time to ctDNA positivity (TTPos) is exponentially distributed, and α=5% (one-sided). The log of the estimated hazard ratio and its' associated standard deviation from a Cox Model will be used to construct a Z-statistic to test the hypothesis. The expected accrue rate is 40/month. Twenty-five months of accrual and 12 additional months of follow-up should provide the needed events. The

critical hazard ratio (decision point to continue to phase III) is 1.48. Fixed parameters are H0, HA, α, and follow-up after accrual.

Patients who are ctDNA(+ve) post-operatively (estimated 30% or 300 patients) or are noted to be ctDNA(+ve) on serial surveillance (estimated 51 patients) will be randomized 1:1 to standard of care adjuvant chemotherapy or the FOLFIRINOX experimental arm. The experimental arm will be compared to control at α=15%, one-sided (H0: 3-year DFS 40% on both arms) by the stratified log rank test. This yields 91% power for a 33.3% reduction in the rate of DFS events (HA: hazard ratio 0.667 or 40% vs 54.3% 3-year DFS). One hundred thirty-seven DFS events are required, and we anticipate 350 patients (including 51 originally in the ctDNA(-ve) cohort) accrued over 25 months and followed 12 additional months will provide the needed events. The number of patients crossing over takes the expected number of patients tuning positive on the experimental arm of the ctDNA-ve cohort under HA and then deducts 25% for metastasis at the time of ctDNA positivity (not eligible to cross over) and 5% more for patients who do not wish to consent to cross over. We further assumed a 1% annual lost to follow-up rate. The critical hazard ratio (decision point to continue to phase III) is 0.838. Fixed parameters are H0, HA, α, power, and follow-up after accrual.

The above scenarios assume 30% of eligible patients will be ctDNA(+ve) post-surgery. This proportion is not known precisely, and we wish to ensure adequate power in the ctDNA+ve cohort. Therefore, we will screen patients in phase II as illustrated in Table 18:

Table 18. Phase II Power

ctDNA+ve Rate	Total N	Months of accrual	Months to phase II answer	Power ctDNA+ve cohort when α=0.15	Power ctDNA-ve cohort	Number initially ctDNA+ve	Number converting -ve to +ve to be rand
0.30	1000	25	37	0.91	0.91	300	51
0.25	1080	27	39	0.90	0.95	270	61
0.20	1160	29	41	0.89	0.97	232	73

Power for the non-inferiority comparison in the ctDNA(-ve) cohort will increase with sample size.

There will be an accrual hiatus of at least a year while we wait for the phase II results.

Phase III:

One or both of the cohorts may be positive in phase II and continue to phase III. We assume the registration and screening for post-op ctDNA will continue if any cohort proceeds to phase III. Here we treat the cohorts separately for the phase III sample size justification.

For the ctDNA(-ve) cohort, the primary endpoint for phase III is DFS in a non-inferiority design. Assuming a null hypothesis of inferiority, H0: 85% DFS at 3 years for mFOLFOX6, 74.6% delayed (HR=1.80); and an alternative hypothesis of a small detriment with delayed chemo HA 85 vs 82.1% DFS at 3 years (HR=1.21)). We further assume time to DFS event is exponentially distributed α=2.5% one-sided, 90% power to infer non-inferiority under HA and a 1% annual lost to follow-up rate. The log of the estimated hazard ratio from a stratified Cox model and its' associated standard deviation will be used to construct a Z-statistic to test the hypothesis. The rate at which ctDNA(-ve) patients accrue will vary with their proportion in patients under study. Table 19 describes the phase III designs as a function of the ctDNA(-ve) rate:

Table 19. Cohort A Phase III Power

ctDNA-ve Rate	Phase II N	Months Phase II Accrual	Months of Accrual Hiatus	Months Phase III Accrual	Phase III Total N	Months to phase III answer
0.70	700	25	14	24	1372	76
0.75	810	27	14	20	1410	73
0.80	928	29	14	11	1280	66

For the ctDNA(+ve) cohort, the primary endpoint for phase III is DFS in a superiority design. Assuming a null hypothesis of H0: 3 year DFS 40% on both arms (HR=1.0); and an alternative hypothesis of a 33.3% reduction in the rate of DFS events (HA: hazard ratio 0.667 or 40% vs 54.3% 3 year DFS). We further assume DFS is exponentially distributed, 1-sided $\alpha = 2.5\%$, and 90% power to infer superiority under HA. The stratified logrank test will be used to test the hypothesis. The rate at which ctDNA(+ve) patients accrue will vary with their proportion in patients under study. Table 20 describes the phase III designs as a function of the ctDNA+ve rate in the study population, but ignores the possibility of additional patients coming in from phase III accrual to the ctDNA(-ve) cohort, being randomized to delayed chemo, and then converting to ctDNA(+ve). The power will be slightly increased if both cohorts accrue in phase III.

Table 20. Cohort B Phase III Power

ctDNA+ve Rate	Phase II N	Months Phase II Accrual	Months of Accrual Hiatus	Months Phase III Accrual	Phase III Total N	Months to phase III answer
0.30	351	25	14	12	540	58
0.25	331	27	14	12	502	63
0.20	305	29	14	13	470	69

The above calculation didn't account for the time needed at the beginning of the trial to ramp up to the expected accrual rate. We expect that this will take about 4 months. Therefore, the timeline listed above will be delayed by 4 months. Maximum expected accrual is 1912 (top rows of Tables 19 and 20) at an expected accrual rate of 40 eligible patients per month and accounting for expected accrual hiatus and accrual ramp up, we anticipate the primary analysis will occur 6 years and 8 months after study initiation.

14.8 Phase III Interim Analysis

An interim analysis of futility will be carried out in each study Cohort at their respective 50% information time.

14.8.1 Interim futility analysis of the superiority phase III trial (Cohort B)

The final analysis of Cohort B will be performed when 257 events were obtained and an interim futility analysis will be performed when 129 events were observed. We will adopt the interim futility stopping rule suggested by Wieand et al. 1994 (Wieand 1994), that is, we will stop the trial for futility if the hazard rate for the Arm 4 is higher or equal to that of Arm3, which indicated that the elevated chemo arm is no more effective than the standard care arm. By using this procedure at 50% information time, with overall power of 0.9 (1-sided α=0.025), we will control

the probability of wrongfully terminate the trial for futility under the alternative (HR=0.67) at 0.011 (Anderson 2011).

14.8.2 Interim futility analysis of the non-inferiority phase III trial (Cohort A)

The final analysis of Cohort A will be performed when we obtain 266 events. We will apply similar futility monitoring rule as described above for the non-inferiority portion of the trial (Cohort A) as suggested by Korn and Freidlin 2018 (Korn 2018). At 50% information time (133 events), we will stop the trial for futility if we observe a $HR \geq 1.8$. Again, this is equivalent to performing a test of the hypothesis HR=1.21 vs. the alternative HR>1.21 and conclude futility if the p-value is <0.011. This will again ensure that the probability of terminating the trial for futility when the HA (HR=1.21) is true is no bigger than 0.011.

14.9 Statistical Analysis Plan

14.9.1 Analysis of Primary Endpoints

14.9.1.1 Cohort A Phase II (TTPos)

The analysis will take the form of a non-inferiority test, α=0.05.

We define delayed adjuvant therapy (Arm 2) to be inferior if H0, HR≥1.9 is true. The test will be conducted by estimating $\hat{\theta} = log(\widehat{HR})$ and its' associated standard deviation $s(\hat{\theta})$from a Cox proportional hazards model stratified on disease stage (Stage III vs. Stage IV) and intended FP chemotherapy (5-FU vs. Capecitabine). The inferior (null) hypothesis is rejected if

$$Z = \frac{\hat{\theta} - log(1.9)}{S(\hat{\theta})} < z_{0.05}.$$

Otherwise, our conclusion will be that we have been "unable to rule out that the delayed strategy is non-inferior than the immediate adjuvant therapy. The analysis will be performed when 173 events are observed. Using the approximation $s(\hat{\theta}) \approx 2/\sqrt{173} = 0.152$, it follows that non-inferiority will be claimed if the estimated HR <1.48.

We will also compute the Kaplan-Meir curves to describe the distribution of TTPos. A summary HR and confidence intervals for TTPos will be computed from the Cox proportional model with treatment arm as the only covariate.

14.9.1.2 Cohort A Phase III (DFS)

This is also a non-inferiority analysis (α=0.025). Similar strategy as outlined in section 14.8.1.1 will be applied. The HR under the null is 1.8. The analysis will be conducted when 268 DFS events are observed. Again, denote $\hat{\theta} = log(\widehat{HR})$ and its' associated standard deviation $s(\hat{\theta})$ estimated from a Cox proportional hazards model stratified on disease stage (Stage III vs. Stage IV) and intended FP chemotherapy (5-FU vs. Capecitabine). The inferior (null) hypothesis is rejected if

$$Z = \frac{\hat{\theta} - log(1.8)}{S(\hat{\theta})} < z_{0.025}.$$

Following the same calculation described in 14.8.1.1, non-inferiority will be claimed if the estimated HR <1.42.

14.9.1.3 Cohort B Phase II & III (DFS)

DFS between the two treatment arms (Arm 3 and Arm 4) will be compared by the stratified log-rank test (1-sided α=0.15 for phase II and 1-sided α=0.025 for phase III). The stratification factors are intended FP chemotherapy (5-FU vs. Capecitabine) and the initial post-op ctDNA source and results (off-study test vs. on-study +ve vs. on-study -ve). Kaplan-Meir curve will be provided and a summary HR and associated 95% confidence interval will be computed from a Cox proportional hazard model with treatment arm as the only covariate.

14.9.2 **Analysis of Secondary Endpoints**

- Incidence (presence) of ctDNA in blood following resection of stage III colon cancer will be monitored continuously. The incidence rate be calculated and corresponding 95% confidence interval will be reported together with the primary analysis of phase II portion of the trial.
- Overall survival (OS) according to cohort and treatment.
  Kaplan-Meier's method will be used to describe the distribution of OS in each group (per cohort and treatment). Stratified log-rank tests and Cox proportional models will be used to compare different arms and estimate hazard ratio.
- Time to recurrence (TTR) according to cohort and treatment.
  Kaplan-Meier's method will be used to describe the distribution of TTR in each group (per cohort and treatment). Stratified log-rank tests and Cox proportional models will be used to compare different arms and estimate hazard ratio.
- To assess the compliance of adjuvant chemotherapy in each arm percentage of patients who completed all planned therapy will be reported. Range and median number of cycles for each adjuvant chemotherapy will also be reported.

14.9.3 **Analysis of Exploratory Endpoints**

- To explore ctDNA kinetics post-surgical resection of high risk stage II (ctDNA +ve) and stage III colon cancer and its association with prognosis.

  Quantitative ctDNA level over time will be described using plots and descriptive statistics. Clustering analysis will be used to identify subgroups of patients based on the ctDNA level over time and Cox proportional hazard model will be used to assess the association between the ctDNA profile and time to event outcomes (RFS, OS and TTR).
- To characterize genomic profiles and its association with TTR using a ctDNA assay in patients with resected colon cancer.

  Genomic profile at baseline will be described as frequencies of genetic variance discovered in primary tumors. Presence and disappearing of genetic mutations over time and its association with TTR will be evaluated by Cox proportional hazard model.

14.9.4 **Toxicities**

Analysis of CTCAEs (version 5.0) will be performed as part of the safety analyses. Within each cohort, the maximum grade of toxicity for each category of interest will be recorded for each patient and the summary results will be tabulated by category and grade for each treatment arm. The tabulations will also be reviewed on a semi-annual basis by the Data Safety Monitoring Board (DSMB).

14.9.5 **Monitoring/Oversight Committee**

NRG Oncology Data Monitoring Committee (DMC)

The NRG Oncology DMC will review the study twice a year with respect to patient accrual and AEs. The DMC also will review the study for protocol-specified interim analyses and on an "as needed" basis.

14.10 **Gender/Ethnicity/Race Distribution**

Table 21. Expected racial and ethnic composition of NRG-GI008 assuming both cohorts proceed to phase III.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	7	7	0	0	14
Asian	42	42	0	0	84
Native Hawaiian or Other Pacific Islander	7	7	0	0	14
Black or African American	114	114	0	0	228
White	444	444	72	72	1032
Other	27	27	0	0	54
Total	641	641	72	72	1426

Table 22. Expected racial and ethnic composition of NRG-GI008 assuming both cohorts proceed to phase III.

INTERNATIONAL PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	3	3	0	0	6
Asian	15	15	0	0	30
Native Hawaiian or Other Pacific Islander	3	3	0	0	6
Black or African American	39	39	0	0	78
White	149	149	24	24	346
Other	10	10	0	0	20
Total	219	219	24	24	486

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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 CTCAE v5.0 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
RECOMMENDED 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.
  - 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.

Irinotecan-induced diarrhea management

- Early onset (within 24 hours of administration)
  - Often immediate onset during or following irinotecan administration
  - May be accompanied by other cholinergic symptoms (abdominal cramping, lacrimation, salivation)
  - Typically responds to atropine (0.25 to 1 mg SC or IV)
- Delayed onset (>24 hours after administration)

  Loperamide 4 mg PO initially, then 2 mg every two hours or 4 mg every four hours until diarrhea free for 12 hours

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, applesauce, and/or toast.

APPENDIX C

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.

Administration (per institutional practice with guidance below):

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 for all chemotherapy in this protocol 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 D

PATIENT DIARY

Protocol: NRG-GI008 **Study Medication: Capecitabine**

Cycle #_____

Prescribed dose: capecitabine _____mg twice each day on days 1 to 14 of each 21 day cycle

- Please record information daily.
- Use a new page for each week.
- Take capecitabine in the morning and evening (within 30 minutes after eating breakfast and dinner). Do not cut or crush tablets.
- Please remember to bring this diary (all pages) and your capecitabine containers (even if they are empty) to each visit with your study team.

Date	**Time taken**		**Number of capecitabine tablets taken (morning)**		**Number of capecitabine tablets taken (evening)**		**Notes**
	Morning	**Evening**	**150mg**	**500mg**	**150mg**	**500mg**	**Include any side effects that you are having (especially loose stools and any medications that you took for the side effects.**

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: _____