NRG ONCOLOGY
NRG-GI005

(ClinicalTrials.gov NCT-04068103)

Phase II/III Study of Circulating tumOr DNA as a Predictive BiomaRker in Adjuvant Chemotherapy in Patients with Stage IIA Colon Cancer (COBRA)

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

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NRG ONCOLOGY
NRG-GI005

Phase II/III Study of Circulating tumOr DNA as a Predictive BiomaRker in Adjuvant Chemotherapy in Patients with Stage IIA Colon Cancer (COBRA)

Protocol Agents

Agent	Supply	NSC #	IND*	IDE #	IDE Sponsor
Oxaliplatin	Commercial	266046	N/A	G190082	Guardant Health
5-Fluorouracil	Commercial	19893			
Leucovorin	Commercial	3590			
Capecitabine	Commercial	712807			
Levoleucovorin	Commercial	807037			

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

Participating Sites

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

Document History

	Version Date
Amendment #1	April 7, 2021
Pre-activation Revision 2	September 16, 2019
Pre-activation Revision	March 14, 2019
Initial	December 5, 2018

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN), which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave®. Please see the data submission section of the protocol for further instructions Do NOT submit study data or forms to CTSU Data Operations. Do NOT copy the CTSU on data submission.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member website located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e., patient eligibility or treatment-related), contact the Clinical Coordinating Department at NRG Oncology at 1-800-477-7227 or by e-mail at ccdPGH@nrgoncology.org		
For non-clinical questions (i.e., unrelated to patient eligibility or treatment), contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923 or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. **For clinical data submission questions**, contact the GI005 Data Manager at the NRG Oncology Statistics and Data Management Center by calling 412-624-2666.		
The CTSU website is located at https://www.ctsu.org.		

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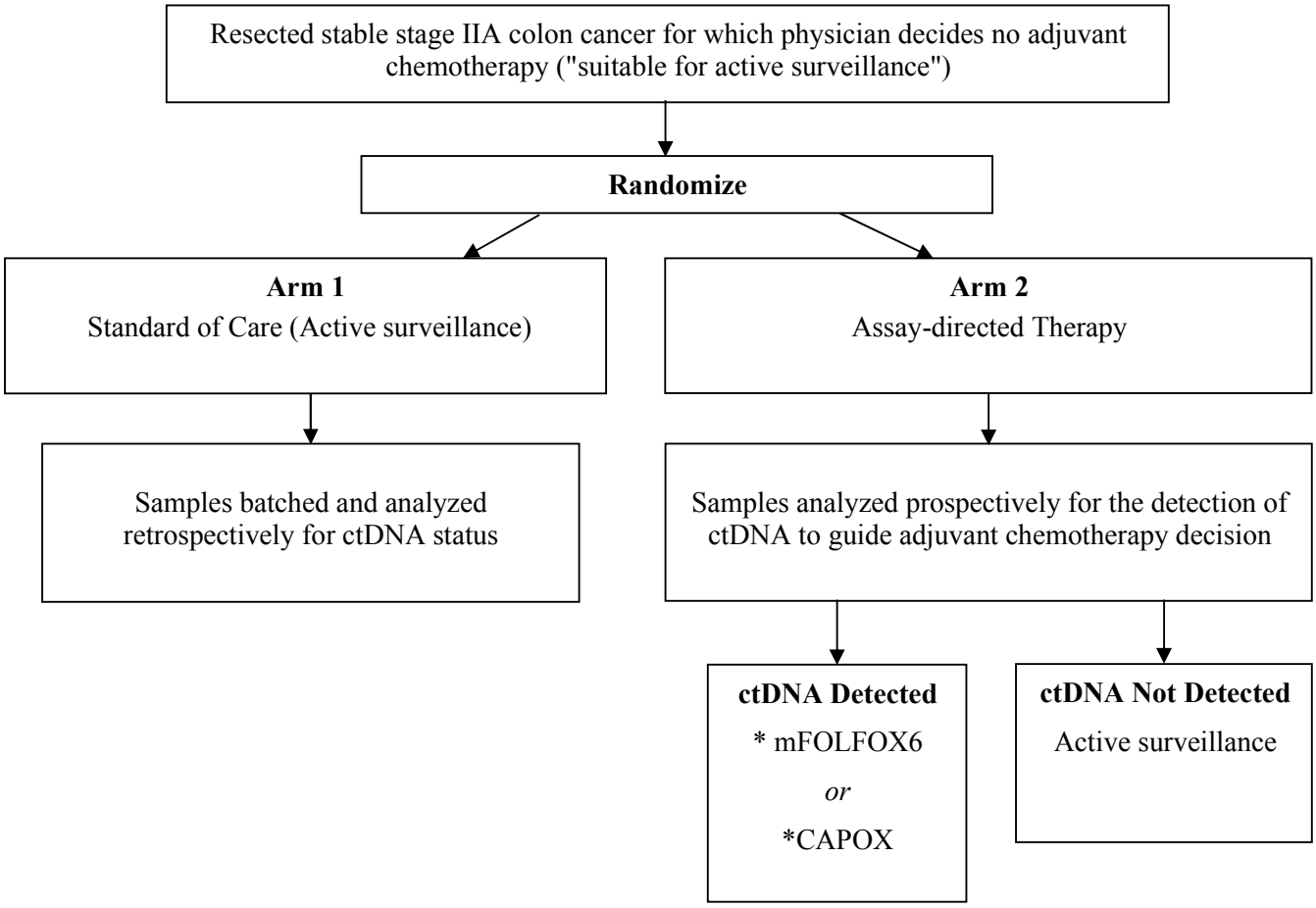
Figure 1. NRG-GI005 Schema



***Acceptable regimens for Arm 2 patients with "ctDNA detected" are:**

- mFOLFOX6: oxaliplatin 85 mg/m^2 IV Day 1 + leucovorin 400 mg/m^2 IV Day 1 + 5-fluorouracil (5-FU) 400 mg/m^2 IV bolus Day 1 followed by 5-FU 2400 mg/m^2 continuous infusion over 46 hours every 2 weeks for twelve cycles

  or

- CAPOX: Oxaliplatin 130 mg/m^2 IV over 2 hours on day 1 + capecitabine 1000 mg/m^2 PO BID on days 1-14 every 3 weeks for eight cycles

1.0 OBJECTIVES

1.1 Primary Objectives

1.1.1 Primary Objective Phase II

To compare the rate of ctDNA clearance in "ctDNA detected" patients treated with or without adjuvant chemotherapy following resection of stage IIA colon cancer.

1.1.2 Primary Objective Phase III

To compare recurrence-free survival (RFS) in "ctDNA detected" patients treated with or without adjuvant chemotherapy following resection of stage IIA colon cancer.

1.2 Secondary Objectives

1.2.1 To describe the prevalence of detectable ctDNA in patients with stage IIA colon cancer following surgical resection.

1.2.2 To estimate time-to-event outcomes (overall survival [OS], recurrence-free survival [RFS], and time to recurrence [TTR] by ctDNA marker status and treatment for patients with resected stage IIA colon cancer.

1.2.3 To estimate the rate of compliance with adjuvant chemotherapy and/or active surveillance for patients with resected stage IIA colon cancer.

1.3 Exploratory Objectives

1.3.1 To describe the association of quantitative ctDNA levels 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 stage IIA colon cancer.

1.3.3 To model the cost effectiveness of the use of ctDNA versus standard of care in this setting.

1.3.4 To evaluate performance of a ctDNA assay after incorporation of patient tumor and peripheral blood mononuclear cells.

2.0 BACKGROUND

2.1 Introduction

Multiple series, from SEER databases, academic centers, and community oncology practices, have reported rates of adjuvant chemotherapy treatment in 25-30% of patients with stage II colon (non-rectal) cancer in the United States (O'Connor 2011; Schrag 2002; Kumar 2015). NCCN Guidelines for patients with stage II colon cancer recommend several acceptable management approaches following resection (i.e., observation, adjuvant chemotherapy, or clinical trial) based upon assessment by the medical oncologist of prognostic tumor characteristics (NCCN Guidelines [Colon Cancer]). Nonetheless, the decision of whether or not to recommend adjuvant chemotherapy for patients with stage II colon cancer deemed low-risk for recurrence remains highly variable among providers. This lack of consistency in (1) the decision whether or not to give chemotherapy and (2) if given, what regimen to administer (e.g., 5-fluorouracil with or without oxaliplatin) is driven by patient factors, pathologic characteristics of the tumor, and physician preference. Current guidelines recommend that a personalized risk stratification approach is taken, generating subjectivity in the treating physician's interpretation of when to offer adjuvant chemotherapy in patients with stage II colon cancer at "low risk" for recurrence. *Validated*, *objective* parameters for deciding whom to recommend adjuvant chemotherapy for stage II colon cancer are lacking.

Arising from tumor cell secretion and apoptosis, circulating tumor DNA (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 high specificity and high sensitivity. Detection of ctDNA following resection across all stages of colon cancer has been demonstrated as a strong prognostic biomarker for tumor recurrence.

An Australian study analyzed 230 patients with stage II colon cancer who had identifiable mutations using a ctDNA next-generation sequencing (NGS) panel on blood collected 4-10 weeks after surgical resection (Tie 2016). 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. 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, independent of traditional clinical risk factors.

These findings were validated in another dataset of patients with resected stages II and III colon cancers. Here, employing another NGS plasma assay (Roche Avenio) corroborated the use of ctDNA technology as a method to identify patients with colon cancer at high risk for recurrence Diehn 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.

As the prognostic implications of remnant ctDNA may surpass those typically considered to classify a patient as having a “high risk” stage II colon cancer, these data suggest that "ctDNA detected" is associated with a high probability for recurrence, warranting consideration of adjuvant chemotherapy for “high risk” stage II colon cancer. If detectable ctDNA is considered a surrogate for micrometastatic disease, it remains unclear whether or not early intervention may improve survival outcomes or hasten toxicity relative to standard radiographic detection of (recurrent) macrometastatic colon cancer.

2.2 Guardant Health LUNAR Assay

The Guardant LUNAR assay is a next generation sequencing-based diagnostic test developed by Guardant Health for the qualitative detection of cancer-derived circulating tumor DNA in EDTA-anticoagulated peripheral whole blood. Briefly, plasma is isolated from whole blood collected in Streck cell-free DNA blood collection tubes, ctDNA is isolated, processed, and sequenced on an Illumina platform. Sequencing data are then analyzed using proprietary bioinformatics algorithms trained to detect the presence of ctDNA based on multiple analytical features, including somatic variation and epigenetic signals, and exclude common sources of interference such as inflammation and clonal hematopoiesis. Based on this analysis, the Guardant LUNAR test returns a result of ctDNA detected or not detected. No somatic or germline genotyping results are reported.

Thus, for patients with colorectal cancer undergoing definitive resection, regardless of the stage of disease, this ctDNA biomarker may potentially identify patients who would benefit the most from systemic adjuvant treatment, even in the absence of other clinical features traditionally considered high-risk. However, use of ctDNA technology is limited by the absence of prospective data for demonstrating benefit as a predictive biomarker for adjuvant chemotherapy. With the rapid evolution of ctDNA use in the clinical management of solid tumors, it is possible that Guardant Health may develop different methodologies for subsequent generations of ctDNA assays in the coming years. Nonetheless, for the duration of the study, the assay proposed here will be fixed/not permitted to be changed for analyses of all study objectives. Collection of additional blood samples at each time point will allow for availability of specimens to be examined in the future by alternative assays outside the context of this study. In addition, with the prognostic implications of detectable ctDNA as a surrogate for minimal residual disease, this technology has the potential to provide clinicians with an objective assay to identify patients at high risk for recurrence following resection. We hypothesize that the detection of ctDNA may provide an objective endpoint for identifying patients with stage IIA colon cancer at high-risk for recurrence following resection that have the most potential to benefit from adjuvant chemotherapy.

3.0 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

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

Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of mFOLFOX6 or CAPOX, when deciding if a patient is an appropriate candidate for this trial.

Submission of blood samples for ctDNA analysis, archived resected primary tumor tissue (FFPE), and uninvolved margin of resection (normal tissue) is **required for all patients**. In addition, all patients will be asked to consent to the submission of optional blood and tumor tissue samples for future research.

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

3.1 Eligibility Criteria

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

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

3.1.2 Age ≥ 18 years at diagnosis.

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

3.1.4 Histologically/pathologically confirmed stage IIA adenocarcinoma of the colon (T3, N0, M0) with at least 12 lymph nodes examined at the time of surgical resection.

3.1.5 Appropriate for active surveillance (i.e., no adjuvant chemotherapy) at the discretion of and as documented by the evaluating oncologist based on current practice patterns.

3.1.6 The distal extent of the tumor must be ≥12 cm from the anal verge on pre-surgical endoscopy (i.e., excluding rectal adenocarcinomas warranting treatment with chemoradiation). If the patient did not undergo a pre-surgical endoscopy, then the distal extent of the tumor must be ≥12 cm from the anal verge as determined by surgical examination or pre-operative imaging.

3.1.7 The patient must have had an en bloc complete gross resection of tumor (curative resection) as definitive surgical cancer treatment within 14 to 60 days of study randomization. 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.

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

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

- Absolute neutrophil count (ANC) must be ≥ 1200/mm^3;
- Platelet count must be ≥ 100,000/mm^3; and
- Hemoglobin must be ≥ 9 g/dL.

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

- total bilirubin must be ≤ ULN (upper limit of normal) for the lab unless the patient has a chronic grade 1 bilirubin elevation due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; *and*
- alkaline phosphatase must be < 2.5 x ULN for the lab; *and*
- AST and ALT must be < 1.5 x ULN for the lab.

3.1.11 Adequate renal function within 28 days before 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

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

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

3.1.13 Patients receiving a coumarin-derivative anticoagulant must agree to weekly monitoring of INR if they are randomized to Arm 2 and receive capecitabine.

3.2 Ineligibility Criteria

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

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

3.2.2 Pathologic, clinical, or radiologic evidence of overt metastatic disease. This includes isolated, distant, or non-contiguous intra-abdominal metastases, even if resected (including the presence of satellite nodules constituting N1c disease in the absence of lymph node involvement).

3.2.3 Tumor-related bowel perforation.

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

3.2.5 History of organ transplantation.

3.2.6 Any prior systemic chemotherapy, targeted therapy, or immunotherapy; or radiation therapy administered as treatment for colorectal cancer (e.g., primary rectal adenocarcinomas for which treatment with neoadjuvant chemoradiation is warranted are not permitted).

3.2.7 Other invasive malignancy within 5 years before randomization. Exceptions are colonic polyps, non-melanoma skin cancer or carcinoma-in-situ including those of the cervix and breast (DCIS).

3.2.8 Synchronous primary rectal and/ or colon cancers.

3.2.9 Antineoplastic therapy (e.g., chemotherapy, targeted therapy, or immunotherapy) within 5 years before randomization. (For the purposes of this study, hormonal therapy is not considered chemotherapy.)

3.2.10 Uncontrolled cardiac disease, in the opinion of the treating medical oncologist, that would preclude the use of any of the drugs included in the GI005 treatment regimen. This includes but is not limited to:

- Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling temporary pacemaker.
- Ventricular tachycardia or supraventricular tachycardia that requires treatment with Class Ia antiarrhythmic drugs (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic drug (e.g., sotalol, amiodarone, dofetilide). Use of other antiarrhythmic drugs is permitted.

- Second- or third-degree atrioventricular (AV) block unless treated with a permanent pacemaker.
- Complete left bundle branch block (LBBB) unless treated with a permanent pacemaker

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

3.2.12 Active seizure disorder uncontrolled by medication.

3.2.13 Active or chronic infection requiring systemic therapy.

3.2.14 Known homozygous DPD (dihydropyrimidine dehydrogenase) deficiency.

3.2.15 Pregnancy or lactation at the time of randomization.

3.2.16 Co-morbid illnesses or other concurrent disease that, in the judgement of the clinician obtaining informed consent, would make the patient inappropriate for entry into this study (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).

3.2.17 Prior testing with any available ctDNA test as part of the management of colon cancer is not permitted.

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

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

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

Required Assessments	**Before randomization** *(see footnote **a**)*	
Consent form signed by the patient	X	
History & physical exam**b**	X	Within 28 days
Assessment of concomitant medications**c**	X	
Performance status (Appendix A)	X	
Height & weight	X	
CEA	X	
CBC/differential/platelet count	X	
Total bilirubin/AST/ALT/Alkaline phosphatase	X	
Serum chemistries: glucose, BUN, sodium, potassium, chloride, bicarbonate or carbon dioxide, calcium, serum creatinine	X	
Distant disease staging**d**	X	
Pregnancy test **e**	X	Within 14 days
Mandatory collection of whole blood for ctDNA**f**	X	Before or after randomization
Optional collection of whole blood specimens**f**	X	
Mandatory submission of archived resected primary tumor tissue and uninvolved margin of resection (normal tissue)**f**	X	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 standard of care before obtaining informed consent but within the timeframes outlined in Table 1 may be used rather than repeating required tests.

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 randomization 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 See Section 10.0 and the NRG-GI005 Pathology and Correlative Science Instructions. Mandatory and optional blood specimens cannot be collected until informed consent is obtained.

Table 2. Tests, exams, and other requirements for all patients through Year 3
Note: Arm 2 patients with "ctDNA detected" ONLY, treated with mFOLFOX6 or CAPOX, have treatment related assessments prior to each cycle and approximately 30 days after the last dose of therapy

Required assessments *(See footnote **a**)*	**Arm 1 patients and Arm 2 patients with" ctDNA not detected" ONLY**	**Arm 2 patients with "ctDNA detected" ONLY**		**All patients 9 months from randomization**	**All patients 12 months from randomization through Year 3***
		Within 3 days before Day 1 of each cycle of mFOLFOX6 or CAPOX *(beginning with Cycle 2)*	**30 days (+/-7 days) after the last dose of chemotherapy**		
History & physical exam**b**	X (3 and 6 months from randomization)	X	X		X (every 6 months)
Adverse event assessment**c**		X	X		
CBC/differential/platelet count		X	X		
Total bilirubin/AST/Alk phos Serum chemistries: glucose, BUN, creatinine, sodium, chloride, bicarbonate or carbon dioxide		X	X		
Potassium, magnesium, and calcium		X	X		
INR**d**		X	X		
CEA	X (3 and 6 months from randomization)	X (prior to week 13 and prior to last cycle of chemotherapy)		X	X (12, 18, 24, 30, 36 months from randomization AND at recurrence)
Disease imaging**e**	X (every 6 months for all patients)				
Submission of unstained slides -optional**f**	X (for all patients at time of recurrence, second primary/secondary malignancy)				

Table continued on next page

Table 2. Tests, exams, and other requirements for all patients through Year 3
Note: Arm 2 patients with "ctDNA detected" ONLY, treated with mFOLFOX6 or CAPOX, have treatment related assessments prior to each cycle and approximately 30 days after the last dose of therapy

Required assessments *(See footnote **a**)*	**Arm 1 patients and Arm 2 patients with "ctDNA not detected" ONLY**	**Arm 2 patients with "ctDNA detected" ONLY**		**All patients 9 months from randomization**	**All patients 12 months from randomization through Year 3***
		Within 3 days before Day 1 of each cycle of mFOLFOX6 or CAPOX *(beginning with Cycle 2)*	**30 days (+/-7 days) after the last dose of chemotherapy**		
Whole Blood for ctDNA (mandatory)**g**	X**h** (6 months from randomization)	X**h** (prior to last cycle of chemotherapy)			
Whole Blood (optional)**i**	X (3 and 6 months from randomization)	X (prior to week 13 and prior to last cycle of chemotherapy)			X (12 months from randomization)
Vital Status Update*					X (every 6 months)

a History and physical, blood tests, x-rays, scans, and other testing may be performed more frequently at the discretion of the investigator.
b Updated history and physical with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up.
c See Section 7.0 for adverse events reporting requirements.
d ***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 5.4.8).
e 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.
f Submission of unstained slides from tumor tissue obtained at the time of recurrence, 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-GI005 Pathology and Correlative Science Instructions).

Table continued on next page

Table 2. Tests, exams, and other requirements for all patients through Year 3 *continued*

g Submission of blood for ctDNA analysis is **required for all patients** (see Section 10.0 and the NRG-GI005 Pathology and Correlative Science Instructions).
h Patients who recur or have a second primary/second malignancy prior to 6 months or prior to the last cycle of chemotherapy should have a whole blood draw for ctDNA at that time to replace the 6 months or prior to the last cycle of chemotherapy timepoint.
i ***Requirement for all patients who agreed to optional blood collection and submission*** in the consent form *(*see Section 10.0 and the NRG-GI005 Pathology and Correlative Science Instructions).
***Note:** *Following documented disease recurrence or diagnosis of an invasive second primary/secondary malignancy, tests, exams, and assessments **are not required**; however, patients will continue to be followed for vital status until Year 3 from randomization.*

5.0 TREATMENT REGIMENS

5.1 Regimen for Arm 1 (Active Surveillance) and Arm 2 patients with "ctDNA not detected"

- Patients will enter active surveillance, consistent with standard of care for low-risk patients.
- For Arm 1 patients, ctDNA results will be analyzed as a batch at approximately a quarterly interval, and results will not be reported back to the patient or the enrolling site.

5.2 Treatment regimen for Arm 2 patients with "ctDNA detected"

- Results will be reported as, "ctDNA detected," "ctDNA not detected,", or "Failed" for the presence of ctDNA, respectively, in the initial postoperative sample. "ctDNA detected" results will direct the patient to be treated with chemotherapy (mFOLFOX6 for 12 cycles (24 weeks) or CAPOX for 8 cycles (24 weeks); see Table 3 or Table 4). "ctDNA not detected" will assign the patient to active surveillance. A "failed" assay at baseline will require a blood redraw, and testing should be completed within 4 weeks following randomization.
- Choice of regimen (mFOLFOX6 or CAPOX) is per the investigator.
- Chemotherapy should begin within 4 weeks following randomization and preferably no longer than 12 weeks from surgery.
- Central venous access is strongly recommended for administration of oxaliplatin and for 5-fluorouracil.
- ***Results of laboratory safety assessments are to be reviewed prior to administration of each cycle of adjuvant chemotherapy.***
- Administer mFOLFOX6 in the order listed, but infusion times for all chemotherapy in this protocol are per institutional guidelines.
- Patient treatment setting (inpatient/outpatient) is per institutional guidelines.
- If there are no treatment delays, each mFOLFOX6 cycle = 2 weeks or 14 days, or each CAPOX cycle=3 weeks or 21 days.
- Total suggested duration of treatment is 12 cycles of mFOLFOX6 or 8 cycles of CAPOX.
- Dose reductions/modifications and/or discontinuation of one or both chemotherapeutic agents is permitted at the clinical judgment of the treating medical oncologist and must be documented. If oxaliplatin is prematurely discontinued, it is strongly recommended that 5-fluorouracil (or capecitabine) is continued for the remaining duration of the intended treatment course.

Table 3. Treatment regimen for Arm 2 patients with "ctDNA detected"- (mFOLFOX6)

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)		

Table continued on next page

Table 3. Treatment regimen for Arm 2 patients with "ctDNA detected"- (mFOLFOX6)

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 Arm 2 patients with "ctDNA detected"-(CAPOX)

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

5.3 Dose determinations

5.3.1 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.

5.3.2 Rounding Doses

Follow institutional practice for standard drug rounding.

5.4 Supportive care guidelines for Arm 2 patients with "ctDNA detected"

5.4.1 G-CSF

- Use of growth factor support as primary prophylaxis to prevent neutropenia is discouraged but not prohibited however, **do not administer G-CSF within 24 hours of chemotherapy**. 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.
- Loratadine (10 mg) or similar agents are permitted if pegfilgrastim is used.

5.4.2 Management of anemia

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

5.4.3 Management of diarrhea

Diarrhea is a commonly occurring toxicity with the therapies included in GI005/Arm 2 patients with "ctDNA detected". 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).

5.4.4 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.

5.4.5 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 7 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.

5.4.6 Management of anaphylaxis

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

5.4.7 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.

5.4.8 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.

5.4.9 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.

5.4.10 Participation in Other Trials

If a GI005 patient is considering participation in another clinical trial (including supportive therapy trials), contact the NRG Oncology Clinical Coordinating Department.

5.5 Duration of Therapy

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

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

- Patient non-compliance
- Pregnancy
  - All women of child bearing potential must 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 documented in the Case Report Form (CRF).

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.
- Treatment schedule changes for non-medical reasons: When rescheduling chemotherapy for non-medical adjustments, refer to the memo "Scheduling Protocol Therapy during the Holidays." This memo provides information regarding treatment over holidays/vacations and other non-medical delays (e.g. physician or patient schedules). This memo is updated annually and is posted on the CTSU Web site under the specific protocol memoranda. Any treatment schedule changes for non-medical reasons must be documented in the patient treatment record.
- In the event of disease recurrence or diagnosis of an invasive second primary cancer or secondary malignancy, chemotherapy (mFOLFOX6/CAPOX) as part of this clinical trial will be discontinued; further therapy is at the investigator's discretion. However, patients will continue to be followed off treatment for survival.

6.2 Treatment management for Arm 2 patients with "ctDNA detected" receiving mFOLFOX6

Chemotherapy dose modifications for Arm 2 patients with "ctDNA detected" are detailed in Tables 6 and 7. Dose modifications are based on the dose level changes outlined in Table 5. Additionally, the following mFOLFOX6 dose modification instructions must be followed:

- All doses must be based on the AE requiring the greatest modification.
- Any chemotherapy doses that have been reduced may not be escalated.
- If ≥ grade 2 toxicity occurs ***during the 46-48 hour infusion of 5-FU***, discontinue the infusion and refer to Table 6 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 treatment with mFOLFOX6 must be discontinued for reasons other than disease recurrence or diagnosis of a second primary cancer or secondary malignancy, tests, exams, and assessments and specimen submissions will continue (see Table 2 and Table 11).
- In the event of disease recurrence or diagnosis of an invasive second primary cancer or secondary malignancy during treatment with mFOLFOX6, mFOLFOX6 will be discontinued; further therapy is at the investigator's discretion. However, patients will continue to be followed off treatment for survival (see Table 2). See Table 11 for specimen submission requirements.

Table 5. 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 6. Treatment management for mFOLFOX6 -(See Table 7 for oxaliplatin-specific toxicities.)

Important table instructions:

- All dose modifications for mFOLFOX6 are based on the dose level changes on Table 5.
- 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 Section 5.4.2 for management of anemia.
- Modifications in dose levels apply to 5-fluorouracil and oxaliplatin unless otherwise indicated; leucovorin doses remain unchanged.
- Dose modifications must be based on the AE requiring the greatest modification.

CTCAE v5.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **b**)
Neutrophil count decreased: Grades 2 (ANC 1000-1199/mm^3)	Maintain dose	*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. 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
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

Table 6. 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 a)***	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE ***(See footnote b)***
Investigations (hepatic): **Bilirubin, AST, alk phos**		
Grade 2	Maintain dose *or* ↓ oxaliplatin one dose level	*Hold until bilirubin returns to the* ***baseline grade*** *and AST and alk phos have returned to ≤ grade 1, then:* ↓ oxaliplatin one dose level
Grade 3	↓ 5-FU *and* oxaliplatin one dose level	*Hold until bilirubin returns to the* ***baseline grade*** *and AST and alk phos have returned to ≤ grade 1, then:* ↓ 5-FU *and* oxaliplatin two dose levels *or* discontinue
Grade 4	Discontinue	Discontinue
Febrile neutropenia:		
Grade 3	Maintain dose *or* ↓ one dose level	Maintain dose *or* ↓ one dose level
Grade 4	↓ one dose level *or* discontinue	↓ one dose level *or* discontinue
Infection:		
Grade 2	Maintain dose *or* ↓ one dose level	Maintain dose *or* ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level *or* discontinue	↓ one dose level *or* discontinue
Other clinically significant AEs:[c]		
Grade 2	Maintain dose *or* ↓ one dose level	Maintain dose *or* ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or discontinue	Discontinue

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

b Hold and check weekly. ***With exception of neutrophils and bilirubin, resume treatment when toxicity is ≤ grade 1.*** If toxicity has not resolved after 4 weeks of delay, discontinue mFOLFOX6 (see Section 6.2 for instructions regarding further study treatment).

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

Table 7. Treatment management for oxaliplatin-specific toxicities

Nervous System Disorders		
Paresthesias/Dysesthesias/ Neuropathy (Peripheral motor; Peripheral sensory)	**1-7 day duration**	**> 7 day duration[a]**
Grade 1	Maintain dose	Maintain dose
Grade 2	Maintain dose[a]	Decrease ***oxaliplatin*** one dose level[a]
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 oxaliplatin for ≥ grade 2 neurotoxicity***. When ≤ grade 1, resume treatment with dose modifications. If > grade 1 toxicity persists after 4 weeks of delay, discontinue oxaliplatin. Continue 5-FU + LV while oxaliplatin is held.		

6.3 Treatment management for Arm 2 patients with "ctDNA detected" receiving CAPOX

Capecitabine dose modifications for Arm 2 patients with "ctDNA detected" treated with CAPOX are detailed in Table 9. See Table 7 for oxaliplatin-specific toxicities. Dose modifications are based on the dose level changes outlined in Table 8.

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 treatment with CAPOX must be discontinued for reasons other than disease recurrence or diagnosis of a second primary cancer or secondary malignancy, tests, exams, and assessments and specimen collections will continue (see Table 2 and Table 11).
- In the event of disease recurrence or diagnosis of an invasive second primary cancer or secondary malignancy during treatment with CAPOX, CAPOX will be discontinued; further therapy is at the investigator's discretion. However, patients will continue to be followed off treatment for survival (see Table 2). See Table 11 for specimen submission requirements.

Table 8. CAPOX dose levels

(See Table 7 for oxaliplatin-specific toxicities.)

	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 9. Treatment management for capecitabine (Arm 2 patients with "ctDNA detected")

Important table instructions: • Dose modifications for capecitabine are based on the dose level changes on Table 8. • **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	*Hold until ≥ 1200/mm^3.If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	*Hold until ≥ 75,000/mm^3* *If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Grade 4	*Hold until ≥ 75,000/mm^3* ↓ one dose level
GI: **Diarrhea** *(despite optimal antidiarrheal management)* Grade 2, 3	***Treatment must be held for grades 2 and 3 diarrhea to avoid severe complications.*** 1st occurrence – ↓ one dose level 2nd occurrence –↓ one dose level 3rd occurrence – Discontinue
Grade 4	Discontinue
Mucositis - oral Grade 2	Maintain dose or ↓ 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

Table continued on next page

Table 9. Treatment management for capecitabine (Arm 2 patients with "ctDNA detected") *continued*

CTCAE v5.0 Adverse Event/Grade	Modifications for AEs that REQUIRED DELAY IN TREATMENT
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
* Determination of "clinically significant" AEs is at the discretion of the investigator.	

6.4 Management for all Arm 1 patients and Arm 2 patients with "ctDNA not detected"

Patients will enter active surveillance, consistent with standard of care for low-risk patients (see Table 2).

7.0 ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Study Agents

7.1.1 Investigational agents

There are no investigational agents in NRG-GI005.

7.1.2 Commercial agents

The commercial agents in NRG-GI005 are 5-fluorouracil (NSC #19893), leucovorin (NSC #3590), levoleucovorin (NSC-#807037), oxaliplatin (NSC #266046), and capecitabine (NSC #712807).

7.2 Adverse Events and Serious Adverse Events

7.2.1 Adverse Event Characteristics

CTCAE term (Adverse event [AE] description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 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 web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.2.2 Definition of an adverse event

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

7.2.3 Definition of a serious adverse event

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

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

7.3 Adverse Events for the Study Agents

7.3.1 Commercial agents

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

FOLFOX (5-fluorouracil, leucovorin or levoleucovorin, and oxaliplatin):
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).

CAPOX (capecitabine, oxaliplatin)

7.4 Expedited Reporting of Adverse Events

- All serious adverse events that meet expedited reporting criteria defined in Table 10 will be reported via the CTEP Adverse Event Reporting System (CTEP-AERS), accessed via the CTEP web site, https://ctepcore.nci.nih.gov/ctepaers/public/login. The reporting timelines are outlined in Table 10.
- Submitting a report via CTEP-AERS serves as notification to the NRG Statistics and Data Management Center (SDMC) and satisfies NRG requirements for expedited adverse event reporting.
- In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology SDMC by phone at 412-383-2557**.** An electronic report must be submitted into CTEP-AERS immediately upon re-establishment of the Internet connection.

7.4.1 Expedited reporting methods

- **CTEP-AERS 24-hour Notification:** Per CTEP NCI Guidelines for Adverse Events Reporting, a **CTEP-AERS 24-hour notification** must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS **5 Calendar Day Report** (see Table 10).
- **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 10).
- **Supporting source documentation** is requested for this study by NRG Oncology as needed to complete adverse event review. When submitting supporting source documentation, remove all identifiers and include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. Contact NRG Oncology at 1-412-624-2666 for source documentation assistance.

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

Expedited reporting requirements begin with the administration of the first mFOLFOX6 or CAPOX dose. Expedited reporting requirements for all patients are provided in Table 10.

Table 10. Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Study Therapy[1,2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NRG Oncology) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (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 or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

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

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically 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 electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.
Effective Date: May 5, 2011

7.4.3 Additional protocol-specific requirements or exceptions to expedited reporting

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.

7.4.4 Secondary malignancy

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

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

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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the GI005 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.

7.4.5 Second malignancy

A ***second*** malignancy is a cancer that is unrelated to the treatment of a prior malignancy and is **NOT** a metastasis from the initial malignancy. Second malignancies require **ONLY** routine reporting within the GI005 Follow-up folder in Medidata Rave (see Section 7.6).

7.4.6 Expedited reporting of pregnancy, pregnancy loss, and death neonatal

Any pregnancy, pregnancy loss, or death neonatal occurring in a female patient or partner of a male patient from the time of consent to 3 months following the last dose of chemotherapy must be reported via CTEP-AERS as a medically significant event. Definitions and reporting instruction for these events are provided in the Cancer Therapy Evaluation Program's (CTEP) revised NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 7.0) located at the following CTEP website: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf). Upon learning of a pregnancy, fetal death, or death neonatal that occurs during study or within 3 months following the last dose of chemotherapy the investigator is **required** to:

- Immediately discontinue mFOLFOX6/CAPOX.
- Call the NRG Oncology Clinical Coordinating Department (CCD).
- Within 5 working days of learning of the event, and as required by the NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 7.0):
  - Create and submit a CTEP-AERS report;
  - Complete the Pregnancy Information Form (located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm); and
  - Contact NRG Oncology at 1-412-624-2666 for documentation assistance.
  - The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same **Pregnancy Information Form** used for the initial report.

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 13.0).
- **All ≥ grade 2 adverse events** that occurred during chemotherapy must be reported on the GI005 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 GI005 Adverse Event forms through Medidata Rave must be maintained in the patient's research record.

7.5.2 Schedule for reporting routine adverse events

Adverse events for Arm 2 patients "ctDNA detected" are to be submitted through Medidata Rave, **even if no AEs were experienced by the patient**. Submit the GI005 Adverse Event and Treatment forms at the end of each cycle and 30 days (+/-7) days after the last dose of chemotherapy.

7.6 Reporting Colon Cancer Recurrence and Second Primary Cancer

Report colon cancer recurrence and second primary cancer (a malignancy that is unrelated to the treatment of a prior malignancy and which is not a metastasis from the initial malignancy) within the GI005 Follow-up folder in Medidata Rave. Supporting documentation should be uploaded into the relevant form in the Follow-up folder in Medidata Rave using available upload fields within those forms. Please upload each document into a different upload field, as any later uploads into a given field erases the document that exists there. (See Section 7.4.4 for reporting instructions for ***secondary*** malignancies.)

8.0 REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

8.1 Cancer Therapy Evaluation Program registration procedures

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

In addition, all investigators act as the Site Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).
Additional information is located on the CTEP website at
< https://ctep.cancer.gov/investigatorResources/default.htm >
For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

8.2 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI CTSU.

8.2.1 IRB Approval

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

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

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

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

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

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

8.2.2 **Additional Requirements for Protocol NRG-GI005 Site Registration**

Additional requirements to obtain an approved site registration status include:

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

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 based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
- Enter the protocol number in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select NRG, and protocol number NRG-GI005
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

8.2.4 **Submitting Regulatory Documents**

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

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

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

8.2.5 Checking Your Site's Registration Status

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

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

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

8.3 Patient Enrollment

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

Requirements for OPEN access:

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

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

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

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

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

8.4 Reimbursement

To receive site reimbursement for biospecimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the NRG-GI005 specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement for CTEP funding.

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

8.5 Investigator-Initiated Discontinuation of chemotherapy

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

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

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

8.6 Patient-Initiated Discontinuation of Chemotherapy

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

8.7 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 SDMC), consent withdrawal form is to be completed via the Add-Event function in Medidata Rave.

8.8 ctDNA Testing Outside of the Conduct of the GI005 Study

Patients participating in the GI005 study are permitted to pursue ctDNA testing outside of the conduct of the GI005 study. Patients who elect to pursue ctDNA testing outside the conduct of this study will be allowed to stay on study. Patients will continue to follow study requirements according to the study schedule. Patients in Arm 1 will be monitored for treatment with chemotherapy received outside the conduct of this study.

9.0 DRUG INFORMATION

9.1 Commercial Agents

The commercial study agents are 5-fluorouracil, leucovorin, levoleucovorin, oxaliplatin, and capecitabine. There are no investigational agents for NRG-GI005.

9.1.1 Availability/Supply

5-fluorouracil (NSC #19893), leucovorin (NSC #3590), levoleucovorin (NSC #807037), capecitabine (NSC #712807) and oxaliplatin (NSC #266046) will not be provided and must be obtained by the investigator from commercial supply. Please see Section 5.2 (Table 3) and (Table 4), for administration instructions. Refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for instructions for standard drug preparation, handling, and storage.

9.1.2 Adverse Events

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

10.0 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

10.1 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-GI005. ***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 GI005 consent form.*** Tumor and blood samples for all patients will be collected at the specified timepoints outlined in Table 11.

Table 11. Mandatory and optional sample requirements

Specimen Type	Collection Time Points	Shipping
Archived resected primary tumor tissue and uninvolved margin of resection (normal tissue)(FFPE) (mandatory)**a**	• **All patients** Must be submitted within 60 days after randomization	NSABP Division of Pathology NRG Oncology Biospecimen Bank-Pittsburgh 1307 Federal Street Suite 303 Pittsburgh, PA 15212
Whole blood for ctDNA (mandatory)**b, e**	• **All patients** Baseline (before or after randomization) *Note: Do not ship sample until patient ID is obtained at randomization.*	Guardant Health, Inc. 505 Penobscot Dr. Redwood City, CA 94063
	• **All Arm 1 and Arm 2 patients with "ctDNA not detected"** 6 months from randomization **e** • **Arm 2 patients with "ctDNA detected"** Prior to administration of last cycle of chemotherapy **e**	
Unstained slides at time of recurrence/secondary malignancy (optional)**c**	• **All patients** At recurrence or second primary/secondary malignancy	NSABP Division of Pathology NRG Oncology Biospecimen Bank-Pittsburgh 1307 Federal Street Suite 303 Pittsburgh, PA 15212

Table continued on next page

Table 11. Mandatory and optional sample requirements (*continued)*

Whole blood (optional) **d**	• **All patients** Baseline (before or after randomization) *Note: Do not ship sample until patient ID is obtained at randomization.*	Baylor College of Medicine NRG Oncology Serum Bank Room N1111 One Baylor Plaza Houston, TX 77030
	• **All Arm 1 and Arm 2 patients with <u>"ctDNA not detected"</u>** - 3 months from randomization - 6 months from randomization • **Arm 2 patients with <u>"ctDNA detected"</u>** - Prior to week 13 administration of chemotherapy - Prior to administration of last cycle of chemotherapy	
	• **All patients** - 12 months from randomization	

a Submit an archived paraffin block (FFPE) or one H & E slide with an additional ≥ 15 unstained slides from **resected primary tumor tissue** and submit an archived paraffin block (FFPE) or one H & E slide with at least 15 unstained slides from **an uninvolved margin of resection (normal tissue).**

b Collect four (4) 10 mL Streck cell-free BCT tubes, at each of these 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. *Note*: A failed assay at baseline will require a blood redraw, and testing should be completed within 4 weeks following randomization.

c If a biopsy was done anytime through Year 3 from randomization as part of routine care at the time of disease recurrence 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.

d For patients participating in the optional specimen collection, collect five (5) 10 mL purple top tubes (EDTA) before or after 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.

e Patients who recur or have a second primary/second malignancy prior to 6 months from randomization or prior to last cycle of chemotherapy should have a whole blood draw for ctDNA at that time to replace the 6 months or prior to last cycle of chemotherapy timepoint.

Note: Refer to the NRG-GI005 Pathology and Correlative Science Instructions for tumor and blood sample collection, alternative sample submission, processing, and submission instructions.

10.2 **Integrated Correlative Studies**

10.2.1 ctDNA Analysis

For all patients enrolled in the study, it is mandatory that blood is collected before randomization and 6 months after randomization specifically to perform necessary ctDNA analyses required for the primary and secondary objectives. Patients who recur prior to 6 months from randomization would have mandatory blood drawn at the time of recurrence in place of the 6-month time point. For those patients randomized to Arm 2, the specimen collected at baseline will be analyzed in near-real-time, with results reported back to sites via SDMC as "ctDNA detected" or ctDNA not detected". All other mandatory specimens will be analyzed in batch processes as part of listed endpoints associated with the study protocol. These results will not be reported back to the patient or the patient's provider.

Additional analyses from all samples will be performed to refine and optimize the Guardant LUNAR test. These analyses include, but are not limited to, assessment of individual genetic and epigenetic signals, ctDNA kinetics with regards to change in variant allele frequency, ctDNA clearance following treatment, analyses of other blood components, and association with patient and tumor characteristics and clinical outcomes.

The Guardant Health LUNAR test is designed to detect mutations and epigenetic signals from circulating tumor DNA agnostic of mutation profiling in associated tumor tissue. However, in order to compare ctDNA findings with those in the corresponding tumor tissue, for all patients enrolled in the study, primary tumor tissue (FFPE) obtained at surgical resection may be utilized in a pre-planned (but retrospective) analysis to explore the representation of genetic and/or epigenetic features in circulation as compared to tissue. This may be used for refinement purposes of assay performance, standards and determination of false positive or false negative ctDNA rates.

10.2.2 Location of testing

Guardant Health, Inc.
505 Penobscot Dr.
Redwood City, CA 94063

10.3 **Exploratory Correlative Studies**

For patients who elect to enroll in the optional biobanking associated with this trial and provide written consent, any additional biospecimen material remaining from the required specimens will be made available for additional research. Funding for the optional tissue biopsy at the time of recurrence will depend upon securing external financial support in the future for prospective collection. However, it is possible that patients may undergo a tissue biopsy for standard-of-care practice at the time of recurrence/progression. If so, one H&E slide and ≥15 unstained slides may be submitted for biobanking, regardless of the securing of external funding. Additional blood samples will be collected and stored for future analyses (See Table 11).

These correlative specimens will serve as an invaluable resource for future ctDNA assay refinement or validation, biomarker discovery, and other analyses associated with personalized treatment determinations. These EDTA specimens will be adequate to allow for analyses of ctDNA kinetics and temporal dynamics associated with clearance, recurrence, and concurrent imaging assessments and exploratory endpoints.

An amendment or proposal for any correlative science studies to be performed on any of these biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of banked tissue 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.

11.0 SPECIAL STUDIES (NON-TISSUE)

Resource utilization, such as anti-cancer therapy, medications, procedures, laboratories, imaging, and hospital stays, will be collected using standard resource utilization data collection forms.

The timing of the collection of utility and resource utilization will be more frequent for some patients when they receive adjuvant chemotherapy and/or at relapse in order to capture adequate data.

The analyses will take the payers' perspective. Discounting will be based on country-specific discounting rate (e.g. 3% in US and 1.5% in Canada) with sensitivity analysis exploring 0%, 1.5%, 3% and 5%.

The robustness of the model results will be assessed using one-way and multi-way sensitivity analyses. Major drivers of medical care costs, namely hospitalization, drugs and survival, will be varied ± 20%, to examine the impact on the base-case incremental cost effectiveness ratios (ICERs). Bootstrapping and the development of a cost-effectiveness acceptability curve will also be conducted to assess the magnitude of uncertainty of the results.

Subgroup analyses based on stratified factors or any future identified clinically beneficial subgroups (either based on clinical factors or biomarkers) will be conducted.

To assess for the cost-effectiveness and the cost-utility of the strategy of testing for ctDNA with a life-time horizon, recognizing that the trial time horizon is 56 months only, a companion state transition model will be constructed with inputs from data collected prospectively in the trial and supplemented by published literature regarding the downstream cost, utility and survival in the recurrent/advanced health states. Probabilistic analysis will be conducted as the base-case and scenario analyses will be conducted for clinically relevant/beneficial subgroups.

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 GI005 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*** non-colon 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 Reporting

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

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

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

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

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

Rave CTEP AERS Integration

The 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.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The

Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

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 (fields added to the form during study build do not need to be query free for the integration call with CTEP-AERS to be a success).

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. 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.

In the rare occurrence, that Internet connectivity is lost; a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

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

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides.

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.

Data Quality Portal

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

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

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

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

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

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 timelier monitoring of patient safety and care. See Sections 7.4 and 7.5 for information about adverse event reporting.

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

13.3 Global Reporting /Monitoring

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

14.0 STATISTICAL CONSIDERATIONS

14.1 Abstract

This is a phase II-III prospectively randomized clinical trial comparing ctDNA assay-directed therapy (chemotherapy for "ctDNA detected" patients, SOC for "ctDNA not detected" patients) to standard of care (SOC, observation after surgery) with equal allocation to treatment arm (1:1). Treatment assignment is not blinded, however, assay results will be blinded for patients assigned to the SOC therapy arm (not assay-directed).

14.2 Endpoint(s)

14.2.1 Primary Endpoints

Phase II: Clearance of ctDNA (to undetectable levels) for the "baseline ctDNA detected" patient subset at 6 months. Patients who recur prior to 6 months should have a blood draw for assessment as soon as possible after diagnosis. Patients with recurrence who fail to provide a blood draw at recurrence will be considered “failure to clear” for analysis purposes.

Phase III: Recurrence-free survival (RFS, time to recurrence or death) for the "baseline ctDNA detected" patient subset. Censoring will be at last patient contact.

14.2.2 Secondary Endpoints

- RFS according to ctDNA marker status and treatment
- Overall Survival (OS) according to ctDNA marker status and treatment
- Time to Recurrence (TTR) according to ctDNA marker status and treatment. Censoring will be at last patient contact or death.
- Compliance with adjuvant chemotherapy and/or active surveillance
- Incidence (presence or absence) of ctDNA in blood following resection of stage II colon cancer

14.2.3 Exploratory Endpoints

- Quantitative ctDNA levels association with time to event outcomes (RFS, OS, and TTR) by treatment received.
- To characterize genomic profiles associated with TTR using a ctDNA assay in patients with resected stage IIA colon cancer.
- Cost effectiveness of the use of ctDNA versus standard of care in this setting.

14.3 Stratification and randomization

There is no stratification on this trial. Patients will be randomized 1:1 between standard of care (Arm 1) and assay-directed therapy (Arm 2). An adaptive randomization scheme that avoids imbalance within participating institutions 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 in the randomizing institution. 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.

14.4 Patient Cohorts

Patients will be analyzed by intention to treat (ITT), that is, patients will be analyzed according to their randomly assigned treatment regardless of treatment actually received. Patients not at risk for recurrence of colon cancer (determined not to have had colon cancer in the first place) will be excluded from the ITT cohort. The "baseline ctDNA detected" cohort is determined by the assay of the pre-randomization blood draw.

14.5 Patient Accrual

We anticipate 4 months of zero accrual after initiation of the study followed by level accrual of 30 patients per month thereafter.

14.6 Sample Size Determination

For this phase II/III study, a total of 1408 patients will be randomized between the two arms in a 1:1 distribution (704 patients/arm) over a period of 47months (30 pts/month). Patients will be followed for an additional 18 months for a total study duration of 65 months. The analysis of RFS between the two arms for the phase III endpoint will occur in the "ctDNA detected" subset (estimated N=76 for both arms combined) when 55 RFS events have been observed. The sample size for this primary phase III analysis was calculated using a one-sided α=.025 and a power of 92%. One percent annual loss to follow-up is assumed for each arm. Here, we assume that 5.45% of patients will be "ctDNA detected", and that untreated patients in this subset will have a 25% RFS at 24 months. We assume that, for the "ctDNA detected" subset, administration of adjuvant chemotherapy will reduce the RFS event rate by 60% (HR .40). The unstratified two-sample logrank test is used for the treatment comparison.

14.7 Study Monitoring

14.7.1 Phase II/III Futility rule

The initial phase II study aims to ascribe the ability of chemotherapy to clear ctDNA in patients with stage IIA colon cancer. When 16 "ctDNA detected" patients have been on study for 6 months (time to complete chemotherapy) and have completed the 6 month blood draw, we will compare the rates of clearance in the "ctDNA detected" patients by arm (assay -directed therapy versus active surveillance). This analysis is anticipated to occur when 540 of 1408 patients have been accrued (~22 months into study). The decision rule is as follows:

- If the p-value from a one-sided Fisher exact test is > 0.35 (i.e., with no improvement in ctDNA clearance definitively detected with chemotherapy), then we will stop early for futility.
- If the p-value is less than or equal to 0.35, then we plan to proceed to the phase III study in order to gather more definitive data on the relationship between treatment and recurrence-free survival. Assuming the 16 "ctDNA detected" patients break down as 8 per arm, this decision rule can be illustrated as follows in Figure 2 where we plot the Fisher's exact p-value as a function of the observed clearance rates in the two arms:
- The operating characteristics of the test are as follows:

P clear control	P clear experimental	Power	Comment
0.1	0.1	7.2%	Null hypothesis
0.1	0.3	46.4%	
0.1	0.4	65.7%	
0.1	0.5	79.1%	
0.1	0.6	90.9%	Alternative hypothesis
0.2	0.2	13.8%	
0.2	0.3	30.0%	
0.2	0.4	45.2%	
0.2	0.5	63.4%	
0.2	0.6	77.3%	

Figure 3: Phase II/III futility rule of ctDNA clearance

						Chemotherapy						
	Number cleared		0	1	2	3	4	5	6	7	8		
		% cleared	0%	13%	25%	38%	50%	63%	75%	88%	100%		
Observation	0	0%	1.0000	0.5000	0.2333	0.1000	0.0385	0.0128	0.0035	0.0007	0.0000		
	1	13%	1.0000	0.7667	0.5000	0.2846	0.1410	0.0594	0.0203	0.0051	0.0007		
	2	25%	1.0000	0.9000	0.7154	0.5000	0.3042	0.1573	0.0660	0.0203	0.0035		**Rule**
	3	38%	1.0000	0.9615	0.8590	0.6958	0.5000	0.3096	0.1573	0.0594	0.0128	Stop futility	p > 0.35
	4	50%	1.0000	0.9872	0.9406	0.8427	0.6904	0.5000	0.3042	0.1410	0.0385	Continue	p <= 0.35
	5	63%	1.0000	0.9965	0.9797	0.9340	0.8427	0.6958	0.5000	0.2846	0.1000		
	6	75%	1.0000	0.9993	0.9949	0.9797	0.9406	0.8590	0.7154	0.5000	0.2333		
	7	88%									0.5000		
	8	100%											

Figure 3: Phase II/III Futility Rule for ctDNA Clearance

Rule illustrated assuming 8 ctDNA+ patient per arm

It is important to note that differences in clearance rates roughly less than 25% correspond to stopping for futility (pink shading), and rate differences below 25% or more (yellow shading) imply continued equipoise as to the value of treatment in this subset.

14.7.2 Interim analysis of the primary phase III endpoint

When 26 RFS events have been observed in the "ctDNA detected" subset (50% information, ~ 40 months), we will compare RFS and proceed if the hazard ratio favors the assay directed therapy arm (Wieand 1994). If the one-sided p-value favoring the assay directed therapy arm is less than 0.001 the DMC will consider a recommendation to stop the trial early for efficacy (Haybittle-Peto rule) (Haybittle 1971).

14.7.3 Monitoring of Patient Accrual

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

14.7.4 Monitoring of Protocol Treatment

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

14.7.5 Further Monitoring

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

All study participants, regardless of arm of randomization or ctDNA status (if tested off protocol), will be monitored for treatment with chemotherapy. If >15% of participants randomized to Arm 1 receive chemotherapy outside of study conduct, then the NRG Oncology DMC will discuss whether or not to continue with study conduct.

14.8 **Analysis**

14.8.1 Primary Endpoints

Phase II: Clearance of ctDNA (to undetectable levels) for the baseline "ctDNA detected" patient subset.

The first 16 patients in the cohort “ctDNA detected” at baseline and the ITT cohort with assay results from the 6-month blood draw or recurrence prior to the 6-month blood draw will be categorized as “cleared” if the 6-month blood draw result is "ctDNA not detected" or “failed to clear” otherwise (assay of "ctDNA detected" or "Failed" or early recurrence). A two by two contingency table of clearance by treatment arm will be created. The one-sided Fisher exact p-value will be used to determine futility based on the rule specified in Section 14.7.1. Degenerate tables where the Fisher p-value cannot be calculated (no patients clear on either arm or all patients clear on both arms) will count as a failure and a recommendation for early termination.

Phase III: Recurrence-free survival

RFS will be compared by treatment arm using the logrank test with no stratification in the ITT cohort. Kaplan Meier curves will be computed to describe the distribution of time to event. A summary hazard ratio and associated confidence interval will be computed from a Cox model with treatment arm as the only covariate.

14.8.2 Secondary Endpoints

- RFS according to ctDNA marker status and treatment
  Kaplan Meier analyses to describe the distribution of time to event for each marker-treatment combination.
- Overall Survival (OS) according to ctDNA marker status and treatment
  Kaplan Meier analyses to describe the distribution of time to event for each marker-treatment combination. The unstratified logrank test will be used to compare treatments for patients “ctDNA Positive” at baseline and a Cox model will estimate the hazard ratio.
- Time to Recurrence (TTR) according to ctDNA marker status and treatment.
  Kaplan Meier analyses to describe the distribution of time to event for each marker-treatment combination. The unstratified logrank test will be used to compare treatments for patients “ctDNA Positive” at baseline and a Cox model will estimate the hazard ratio.

- Compliance with adjuvant chemotherapy and/or active surveillance.
  The duration of chemotherapy will be categorized as None, less than 3 months, and at least 3 months by treatment arm and baseline ctDNA status. Arms will be compared by a chi square test within each baseline ctDNA status.
- Incidence (detection or no detection) of ctDNA in blood following resection of stage IIA colon cancer
- Combined baseline rate of "ctDNA detected" for all patients in the ITT cohort.

14.9 **Gender/Ethnicity/Race Distribution**

Possible racial and ethnic variation assuming 1408 patients are randomized:

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

Table 12. Gender/Ethnicity/Race Distribution

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	3	5	0	0	8
Asian	27	25	0	0	52
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	66	69	0	0	135
White	323	339	85	89	836
More Than One Race	6	6	6	6	24
Total	426	445	91	95	1057

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	25	45	0	0	70
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	2	0	0	3
White	97	180	0	0	277
More Than One Race	0	0	0	0	0
Total	124	227	0	0	351

15.0 REFERENCES

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APPENDIX A

ASSESSMENT OF PERFORMANCE STATUS AND ACTIVITIES OF DAILY LIVING

1.0 PERFORMANCE STATUS

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

2.0 ACTIVITIES OF DAILY LIVING

The following definitions for activities of daily living (ADL) should be used when the CTCAE v5.0 grading criteria are based on ADL:

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

APPENDIX B

CLINICAL MANAGEMENT OF DIARRHEA

Pharmacologic diarrhea management

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

Dietary management

Instruct patients to:

- Stop all lactose-containing products (milk, yogurt, cheese, etc.).
- Drink 8-10 large glasses (64-80 ounces) of clear liquids per day.
- Eat frequent small meals.
- Maintain a low fat diet enriched with rice, bananas, 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. Do not round the dose.

Administration:

Further dilute the reconstituted levoleucovorin dose with 250 mL D5W.

Using separate infusion bags and separate lines utilizing Y-connector tubing, administer levoleucovorin IV over 2 hours concurrently with oxaliplatin (mFOLFOX6). If oxaliplatin is held, administer levoleucovorin over 2 hours (preferred); however, administration time 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-GI005 **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).
- Please remember to bring this diary (all pages) and your capecitabine containers (even if they are empty) to each visit with your study team.

Day	Date	Time taken		Number of capecitabine tablets taken (morning)		Number of capecitabine tablets taken (evening)		Notes
		Morning	Evening	150mg	500mg	150mg	500mg	Include any side effects that you are having (especially loose stools and any medications that you took for the side effects.
Mon.								
Tues.								
Wed.								
Thurs.								
Fri.								
Sat.								
Sun.								

Patient's name: _____ Date: _____

Physician's office will complete this section

Total number of capecitabine tablets taken this reporting period: 150 mg _____500 mg _____

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

Research Staff Signature/Date: _____