Eligibility Criteria

1. The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.
2. The patient must be ≥ 18 years old.
3. The patient must have an ECOG performance status of 0 or 1 (see Appendix A).
4. Patients must have histologically/pathologically confirmed Stage IIIA or Stage IIIB colon adenocarcinoma (T1-3, N1/N1c) with R0 resection accordingly to AJCC 8th edition criteria. NOTE: Patients with pathologic stages II or IIIC colon adenocarcinoma with R0 resection who have a commercially obtained Signatera® ctDNA+ve assay result post-operatively meeting all timelines and eligibility requirements otherwise, are eligible for enrollment and inclusion in Cohort B.
5. No radiographic evidence of overt metastatic disease within 28 days prior to study entry (CT with IV contrast or MRI imaging is acceptable and must include chest, abdomen, and pelvis).
6. The distal extent of the tumor must be ≥ 12 cm from the anal verge on colonoscopy or above the peritoneal reflection as documented during surgery or on pathology specimen (i.e., excluding rectal adenocarcinomas warranting treatment with chemoradiation).
7. The patient must have had an en bloc complete gross resection of tumor (curative resection). Patients who have had a two-stage surgical procedure, to first provide a decompressive colostomy and then in a later procedure to have the definitive surgical resection, are eligible.
8. The resected tumor specimen and a blood specimen from patients with Stage IIIA or Stage IIIB colon cancer must have central testing for ctDNA using the Signatera assay by Natera. NOTE: Patients with stage IIIA or IIIB colon cancer who otherwise meet eligibility criteria and have had ctDNA status checked with the Signatera® assay as routine care outside of the study, are allowed to be enrolled, and will be retested and placed in either Cohort A or Cohort B depending on the central ctDNA testing result.
   NOTE: Patients with stage II or IIIC colon cancer who otherwise meet eligibility criteria and have had ctDNA status checked with the Signatera® assay as routine care outside of the study AND have a ctDNA+ve result, are allowed to be enrolled. Patients will have central ctDNA testing, confirmed to be ctDNA+ve, and placed in Cohort B.
9. Tumor must be documented as microsatellite stable or have intact mismatch repair proteins through CLIA-approved laboratory testing. Patients whose tumors are MSI-H or dMMR are excluded.
10. The treating investigator must deem the patient a candidate for all potential agents used in this trial (5FU, LV, oxaliplatin and irinotecan).
11. The interval between surgery (post-operative Day 7) and study entry must be no more than 60 days.
12. Availability and provision of adequate surgical tumor tissue for molecular diagnostics and confirmatory profiling.
13. Adequate hematologic function within 28 days before study entry defined as follows:
14. Adequate hepatic function within 28 days before study entry defined as follows:
   • total bilirubin must be ≤ ULN (upper limit of normal) for the lab and
   • alkaline phosphatase must be < 2.5 x ULN for the lab; and
   • AST and ALT must be < 2.5 x ULN for the lab.
15. Adequate renal function within 28 days before study entry defined as serum creatinine ≤ 1.5 x ULN for the lab or measured or calculated creatinine clearance ≥ 50 mL/min using the Cockcroft-Gault formula for patients with creatinine levels > 1.5 x ULN for the lab.
   For Women
   Creatinine Clearance (mL/min) = (140 – age) x weight (kg) x 0.85
   72 x serum creatinine (mg/dL)
   For Men
   Creatinine Clearance (mL/min) = (140 – age) x weight (kg)
   72 x serum creatinine (mg/dL)
16. HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
17. Pregnancy test (urine or serum according to institutional standard) done within 14 days before study entry must be negative (for women of childbearing potential only).
18. Patients receiving a coumarin-derivative anticoagulant must agree to weekly monitoring of INR if they are randomized to Arm 1 or Arm 3 and receive capecitabine.

Ineligibility Criteria
1. Colon cancer histology other than adenocarcinoma (i.e., neuroendocrine carcinoma, sarcoma, lymphoma, squamous cell carcinoma, etc.).
2. Pathologic, clinical, or radiologic overt evidence of metastatic disease. This includes isolated, distant, or non-contiguous intra-abdominal metastases, even if resected.
3. Tumor-related bowel perforation.
4. History of prior invasive colon malignancy, regardless of disease-free interval.
5. History of bone marrow or solid organ transplantation (regardless of current immunosuppressive therapy needs). Bone grafts, skin grafts, corneal transplants and organ/tissue donation are not exclusionary.
6. Any prior systemic chemotherapy, targeted therapy, or immunotherapy; or radiation therapy administered as treatment for colorectal cancer (e.g., primary colon adenocarcinomas for which treatment with neoadjuvant chemotherapy and/or radiation is warranted are not permitted).
7. Other invasive malignancy within 5 years before study entry. Exceptions are colonic polyps, non-melanoma skin cancer or any carcinoma-in-situ.
8. Synchronous primary rectal and/or colon cancers.
9. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
10. Sensory or motor neuropathy ≥ grade 2, according to CTCAE v5.0.
11. Blood transfusion within two weeks before collection of blood for central ctDNA testing.
12. Active seizure disorder uncontrolled by medication.
13. Active or chronic infection requiring systemic therapy.
14. Known homozygous DPD (dihydropyrimidine dehydrogenase) deficiency.
15. Patients known to have Gilbert's Syndrome or homozygosity for UGT1A1*28 polymorphism.
16. Pregnancy or lactation at the time of study entry.
17. Co-morbid illnesses or other concurrent disease that would make the patient inappropriate for entry into this study (i.e., unable to tolerate 6 months of combination chemotherapy or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens or prevent required follow-up).

Eligibility Criteria for Cohort A Arm-2 patients on Second Randomization
1. Patient must have developed a ctDNA +ve assay during serial monitoring.
2. Patient's willingness to be re-randomized affirmed.
3. The patient must continue to have an ECOG performance status of 0 or 1 (see Appendix A).
4. No radiographic evidence of overt metastatic disease.
5. Pregnancy test (urine or serum according to institutional standard) done within 14 days before second randomization must be negative (for women of childbearing potential only).
6. Adequate hematologic function within 28 days before second randomization defined as follows:
   • Absolute neutrophil count (ANC) must be ≥ 1500/mm3;
   • Platelet count must be ≥ 100,000/mm3; and
   • Hemoglobin must be ≥ 9 g/dL.
7. Adequate hepatic function within 28 days before second randomization defined as follows:
   • total bilirubin must be ≤ ULN (upper limit of normal) for the lab and
   • alkaline phosphatase must be < 2.5 x ULN for the lab; and
   • AST and ALT must be < 2.5 x ULN for the lab.
8. Adequate renal function within 28 days before second randomization defined as serum creatinine ≤ 1.5 x ULN for the lab or measured or calculated creatinine clearance ≥ 50 mL/min using the Cockroft-Gault formula for patients with creatinine levels > 1.5 x ULN for the lab.
   For Women
   Creatinine Clearance (mL/min) = (140 – age) x weight (kg) x 0.85
   72 x serum creatinine (mg/dL)
   For Men
   Creatinine Clearance (mL/min) = (140 – age) x weight (kg)
   72 x serum creatinine (mg/dL)

Ineligibility Criteria for Cohort A Arm-2 patients on Second Randomization
1. Pregnancy or lactation at the time of second randomization.
2. No longer a candidate for systemic chemotherapy (FOLFOX, CAPOX, and mFOLFIRINOX) in the opinion of the treating investigator.
Figure 1.
NRG-GI008 SCHEMA

Stage III (T1-3, N1/N1c) Resected Colon Cancer or ctDNA +ve Stage II or Stage IIIIC Resected Colon Cancer
• R0 resection
• pMMR / MSS

Step 1-Registration*
Central ctDNA Testing for all patients

Cohort A
cDNA-ve

Cohort B*
cDNA+ve

Stratification
• Stage (IIIA vs IIIB)
• Intended chemo (5-FU vs Capecitabine)

Step 2-Randomization

Arm 1
mFOLFOX6 for 3-6 months or CAPOX for 3 months

Arm 2
Monitored with serial ctDNA testing every 3 months**

Arm 3
mFOLFOX6 or CAPOX for 6 months

Arm 4
mFOLFIRINOX for 6 months