FAST FACTS

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

Eligibility Criteria

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

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

3.0.2 The patient must be ≥ 18 years old.

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

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

3.0.5 No radiographic evidence of overt metastatic disease within 45 days prior to Step 1/Study entry (CT with IV contrast or MRI imaging is acceptable and **must** include chest, abdomen, and pelvis). Patients with a documented history of allergy to contrast dye or decreased renal function (but still meeting eligibility criteria) are allowed to proceed with CT scans without IV contrast.

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

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

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

3.0.9 Tumor must be documented as microsatellite stable or have intact mismatch repair proteins through CLIA-approved laboratory testing or through testing by an accredited laboratory regulated by Canadian provincial health authorities. Patients whose tumors are MSI-H or dMMR are excluded.

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

3.0.11 The interval between surgery (post-operative Day 7) and Step 1/Study entry must be **no**

more than 60 days. Note: Step 1/Study Entry may occur as early as post-operative Day 7, but it cannot occur beyond 60 days from the actual date of the patient's surgery.

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

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

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

3.0.14 Adequate hepatic function within 28 days before Step 1/Study entry defined as follows:

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

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

For Women

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

For Men

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

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

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

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

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

3.1 Ineligibility Criteria

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

3.1.1 Colon cancer histology other than adenocarcinoma (i.e., neuroendocrine carcinoma,

sarcoma, lymphoma, squamous cell carcinoma, etc.).

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

3.1.3 Tumor-related bowel perforation.

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

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

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

Exception: one cycle of chemotherapy (regimen per treating physicians' discretion – 5-FU (2 weeks) or capecitabine (3 weeks) with or without oxaliplatin [see Section 3.1.1]) is allowed but not required after consent. The optional cycle of chemotherapy should be started ≥ 4 weeks from surgery and should be completed before Step 2 randomization.

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

3.1.8 Synchronous primary rectal and/ or colon cancers.

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

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

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

3.1.12 Active seizure disorder uncontrolled by medication.

3.1.13 Active or chronic infection requiring systemic therapy.

3.1.14 Known homozygous DPD (dihydropyrimidine dehydrogenase) deficiency.

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

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

3.1.17 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

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

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

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

3.1.4 No radiographic evidence of overt metastatic disease.

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

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

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

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

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

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

For Women

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

For Men

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

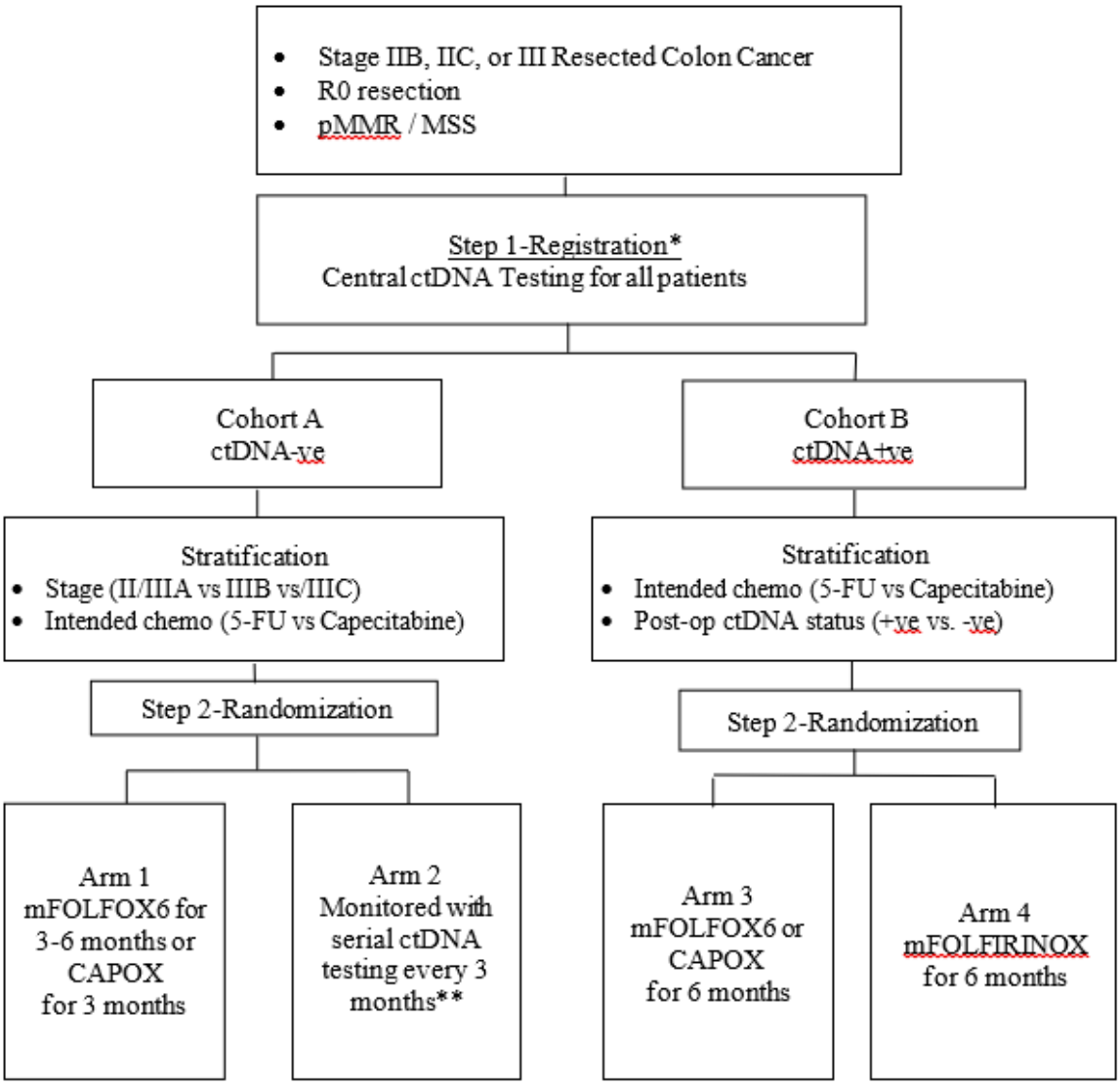
Note: Adjusted body weight (AdjBW) should be used for patients that have BMI ≥ 28 (≥30% above IBW).

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.

NRG-GI008 SCHEMA



* For patients on all arms, one cycle of chemotherapy (regimen per treating physicians' discretion – 5-FU (2 weeks) or capecitabine (3 weeks) with or without oxaliplatin) is allowed but not required after consent. The optional cycle of chemotherapy should be started ≥ 4 weeks from surgery and should be completed before Step 2 randomization. After randomization, refer to the appropriate regimen in Section 5.0.

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