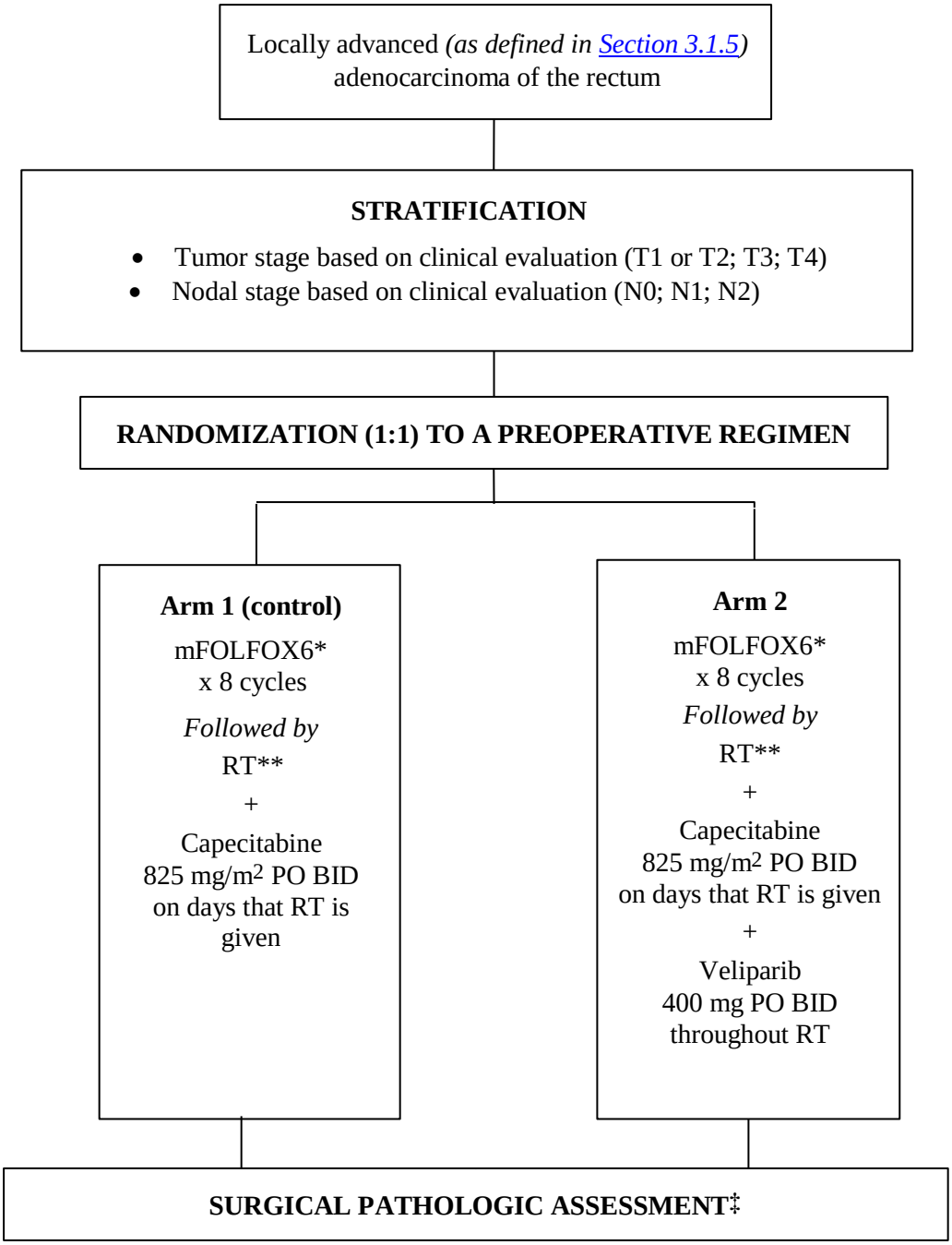
Figure 1. NRG-GI002 SCHEMA



* **modified FOLFOX6 regimen:** oxaliplatin 85mg/m^2 IV Day 1 + leucovorin 400mg/m^2 IV Day 1 + 5-FU 400mg/m^2 IV bolus followed by 5-FU 2400 mg/m^2 continuous infusion over 46 hours every 2 weeks for 8 cycles

** **RT starts 3-4 weeks following last dose of mFOLFOX6**
4500 cGy in 25 fractions over 5 weeks + 540 cGy boost in 3 fractions; IMRT is allowed *(institutional credentialing for IMRT is required)*.

‡ Surgery performed 8-12 weeks following last dose of radiotherapy

Note: Adjuvant therapy is not recommended but allowed (see Section 5.8).

3.0 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

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

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

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

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

3.1 Eligibility Criteria

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

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

3.1.2 Age ≥ 18 years at diagnosis

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

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

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

- distance of the lowest tumor margin from the anal verge; *and*
- intent for sphincter sparing surgical resection or not according to the primary surgeon.

3.1.5 The tumor must be clinically determined to be locally advanced Stage II or Stage III rectal cancer, defined as meeting **any ONE** of the following criteria:

- *distal location (as defined by measurement on MRI, ERUS/pelvic CT [with IV contrast] scan or palpable on digital rectal exam [DRE])*: $cT_{3-4} \leq 5$ cm from the anal verge, any N
- *bulky:* any cT_4 with the majority of the untreated tumor < 12 cm from the anal verge or below the peritoneal reflection as determined by the treating surgeon, or evidence that the tumor is adjacent to (defined as within 3 mm of) the mesorectal fascia on MRI or ERUS/pelvic CT (with IV contrast) scan
- *high risk for metastatic disease* with 4 or more regional lymph nodes (cN_2)
- *not a candidate for sphincter-sparing surgical resection* prior to neoadjuvant therapy (as planned by the primary surgeon)

Note: **Clinical stage of the primary tumor and nodes** may be determined locally by endoscopic ultrasound or abdominal/pelvic MRI (MRI is preferred; see Appendix H). CT scan with IV contrast is acceptable provided there is evidence of T_4 and/or N_2 disease. **Clinical Nodal or "cN"** status for eligibility includes the total number of nodes (N_2 = 4 or more) in the mesorectal and superior rectal stations measuring ≥ 1.0 cm in any axis on cross sectional or endoscopic imaging.

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

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

- ANC must be ≥ 1200/mm^3;
- Platelet count must be ≥ 100,000/mm^3; and
- Hemoglobin must be ≥ 10 g/dL.

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

- total bilirubin must be ≤ ULN (upper limit of normal) for the lab unless the patient has a bilirubin elevation > ULN to 1.5 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; *and*
- alkaline phosphatase must be ≤ 3 x ULN for the lab; *and*
- AST must be ≤ 3 x ULN for the lab.

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

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

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

3.1.11 International normalized ratio of prothrombin time (INR) and prothrombin time (PT) within 28 days before randomization must be WNL for the lab. Patients who are therapeutically treated with an agent such as warfarin may participate if they are on a stable dose and no underlying abnormality in coagulation parameters exists per medical history. (See Section 5.5.8 for coumarin-derivative drug/drug interactions).

3.1.12 Patients with acquired immunodeficiency syndrome (AIDS-related illnesses) or known human immunodeficiency virus (HIV) disease **must**:

- Have a CD4 count ≥ 200 cells/μL within 30 days before randomization,
- Be off all antiretroviral therapy (prophylaxis/treatment) more than 60 days before randomization, *and*
- Have no evidence of opportunistic infections.

3.1.13 Pregnancy test done within 14 days before randomization must be negative (for women of childbearing potential only). Pregnancy testing should be performed according to institutional standards.

3.2 Ineligibility Criteria

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

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

3.2.2 Definitive clinical or radiologic evidence of metastatic disease. Required imaging studies must have been performed within 28 days prior to randomization. ***Note:*** **Distant clinical staging** to exclude patients with overt metastatic disease is determined by CT scan with IV contrast (chest/abdomen/pelvis), with or without PET scan (preferred). MRI of the abdomen and pelvis and a chest x-ray (PA and lateral) is acceptable. *(It is recommended that the same imaging tests that are performed before randomization be used at follow-up time points.)*

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

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

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

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

3.2.6 Active inflammatory bowel disease (i.e., patients requiring current medical interventions or who are symptomatic) or have a history of abdominal surgery that may interfere with gastrointestinal motility or absorption.

3.2.7 Active seizure disorder uncontrolled by medication.

3.2.8 Any antineoplastic therapy for this cancer before randomization.

3.2.9 Synchronous colon cancer.

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

3.2.11 Chemotherapy within 5 years before randomization. (For the purposes of this study, hormonal therapy is not considered chemotherapy.)

3.2.12 Prior treatment with an investigational compound being tested in this study (e.g., PARP inhibitor).

3.2.13 Major surgery within 4 weeks before randomization.

3.2.14 Any therapeutic pelvic radiation.

3.2.15 Known DPD (dihydro pyrimidine dehydrogenase) deficiency.

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

- pregnant women
- nursing women who are unwilling to discontinue nursing
- men or women of childbearing potential who are unwilling to employ adequate contraception (e.g., hormonal or barrier method of birth control; abstinence) for the duration of study treatment and for 3 months after the last dose of study therapy.

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