Cancer Research Consortium of West Michigan
P: 616.391.1230 | 800.336.6299 | www.crcwm.org

FAST FACTS

NSABP PROTOCOL FC-11 - A Phase II Study Evaluating the Combination of Neratinib Plus Trastuzumab or Neratinib Plus Cetuximab in Patients with "Quadruple Wild-Type" (KRAS/NRAS/BRAF/PIK3CA Wild-Type) Metastatic Colorectal Cancer Based on HER2 Status: Amplified, Non-Amplified (Wild-Type) or Mutated

Eligibility criteria

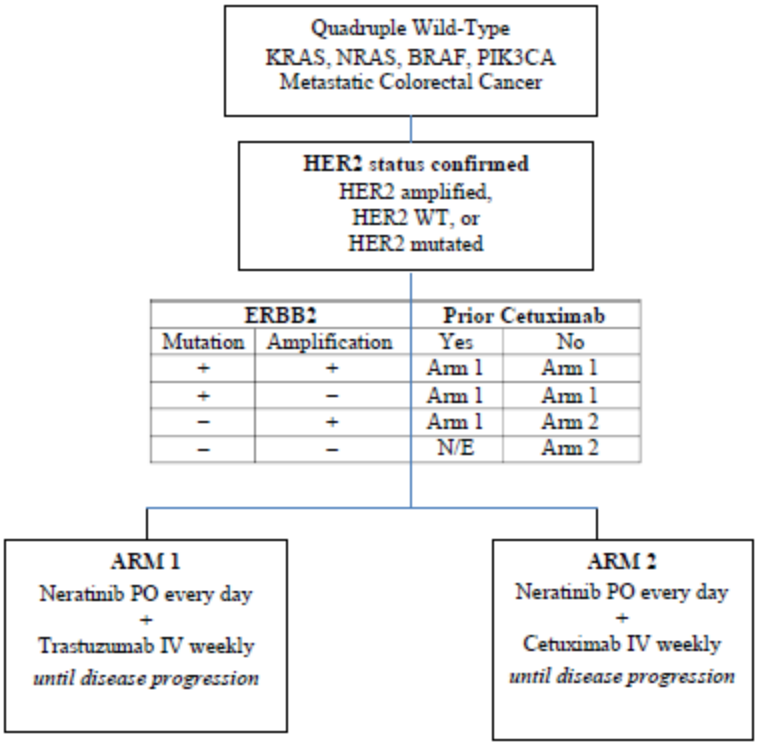
1. The patient must have consented to participate and, prior to study entry, must have signed and dated an appropriate IRB-approved consent form that conforms to federal and institutional guidelines for study treatment.
2. The tumor tissue must have been determined to be KRAS, NRAS, BRAF, PIK3CA (all RAS quadruple) wild-type by CLIA testing.
3. Patients must be ≥ 18 years old.
4. The ECOG performance status must be 0, 1 or 2 (see Appendix A).
5. Patients must have the ability to swallow and retain oral medication.
6. There must be documentation by CT scan, or MRI, that the patient has evidence of measurable metastatic disease per RECIST 1.1 criteria.
7. Patients must have an accessible metastatic lesion for pretreatment core biopsy procurement.
8. Unless either drug is medically contraindicated, patients must have received oxaliplatin and irinotecan as part of standard chemotherapy regimens. (This includes adjuvant therapy.)
9. Specific patient eligibility for quadruple WT and HER2 status:
   • *Arm 1*:
   − HER2 amplified confirmed by CLIA testing performed on blood samples, *and* prior treatment with cetuximab or panitumumab.
   − HER2 mutation (see Appendix B for qualifying mutations) confirmed by CLIA testing, *and* with or without prior treatment with cetuximab or panitumumab.
   • *Arm 2*:
   − HER2 WT or HER2 amplified confirmed by CLIA testing, *and* no prior therapy with cetuximab or panitumumab.
10. Blood counts performed within 2 weeks prior to study entry must meet the following criteria:
    • ANC must be ≥ 1000/mm3
    • Platelet count must be ≥ 75,000/mm3
    • Hemoglobin must be ≥ 8 g/dL.
11. Adequate hepatic function performed within 2 weeks prior to study entry must be met:
    • Total bilirubin must be ≤ 1.5 x ULN (upper limit of normal) for the lab unless the patient has a bilirubin elevation > 1.5 x ULN to 3 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 *with the following exception:* for patients with documented liver metastases or bone involvement alkaline phosphatase must be ≤ 5 x ULN; *and*
    • AST and ALT must be ≤ 3 x ULN for the lab *with the following exception:* for patients with documented liver metastases, AST and ALT must be ≤ 5 x ULN.

12. Serum creatinine performed within 2 weeks prior to study entry must be ≤ 1.5 x ULN for the lab.
13. Patients eligible for Arm 1 (neratinib + trastuzumab): Left ventricular ejection fraction must be ≥ 50% or within normal range for the institution (whichever is lowest). See Section 6.0.
14. Female patients and male patients with female partners of reproductive potential must agree to use an effective method of contraception during therapy and for at least 7 months after the last dose of study therapy.

Ineligible criteria

1. Diagnosis of anal or small bowel carcinoma.
2. Colorectal cancer histology other than adenocarcinoma, e.g., sarcoma, lymphoma, carcinoid.
3. Previous therapy with any HER2 targeting agents (such as trastuzumab, lapatinib, neratinib, etc.) for any malignancy.
4. Symptomatic brain metastases or brain metastases requiring chronic steroids to control symptoms.
5. Active hepatitis B or hepatitis C with abnormal liver function tests.
6. Malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, resection of the stomach or small bowel, or other disease or condition significantly affecting gastrointestinal function.
7. Persistent CTCAE v4.0 ≥ grade 2 diarrhea regardless of etiology.
8. CTCAE v4.0 grade 3 or 4 anorexia or nausea related to metastatic disease.
9. CTCAE v4.0 ≥ grade 2 vomiting related to metastatic disease.
10. Any of the following cardiac conditions:
    • Documented congestive heart failure
    • Myocardial infarction within 6 months prior to study entry
    • Unstable angina within 6 months prior to study entry
    • Symptomatic arrhythmia.
11. Serious or non-healing wound, skin ulcer, or bone fracture.
12. History of bleeding diathesis. (Patients on stable anticoagulant therapy are eligible.)
13. Symptomatic interstitial lung disease or definitive evidence of interstitial lung disease described on CT scan, MRI, or chest x-ray in asymptomatic patients; dyspnea at rest requiring current continuous oxygen therapy.
14. Previous serious hypersensitivity reaction to monoclonal antibodies. (Determination of "serious" hypersensitivity reaction is at the investigator's discretion.)
15. Other malignancies unless the patient is considered to be disease-free and has completed therapy for the malignancy ≥ 12 months prior to study entry. Patients with the following cancers are eligible if diagnosed and treated within the past 12 months: carcinoma in situ of the cervix, colorectal carcinoma in situ, melanoma in situ, and basal cell and squamous cell carcinoma of the skin.
16. Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.
17. Pregnancy or lactation at the time of study entry. ***(Note: Pregnancy testing should be performed within 14 days prior to study entry according to institutional standards for women of childbearing potential.)***
18. Use of any investigational agent within 4 weeks prior to study entry.
    Note: Use of agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors, and proton pump inhibitors (PPIs) should be avoided for the duration of study therapy.

Figure 1.
FC-11 Schema



Study therapy: ***(For each Arm: 1 cycle = 28 days)***

Arm 1:

- Neratinib 240 mg PO daily beginning Day 1 of trastuzumab (Day 1 of Cycle 1)
- Trastuzumab loading dose is 4 mg/kg IV. Subsequent dosing of trastuzumab is 2 mg/kg IV weekly.

Arm 2

- Neratinib 240 mg PO daily beginning Day 1 of cetuximab (Day 1 of Cycle 1)
- Cetuximab loading dose is 400mg/m^2 IV followed by cetuximab 250mg/m^2 IV weekly.

Study therapy will continue until disease progression or intolerable toxicity.