Cancer Research Consortium of West Michigan
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FAST FACTS

S1613 - A RANDOMIZED PHASE II STUDY OF TRASTUZUMAB AND PERTUZUMAB (TP) COMPARED TO CETUXIMAB AND IRINOTECAN (CETIRI) IN ADVANCED/METASTATIC COLORECTAL CANCER (MCRC) WITH HER-2 AMPLIFICATION

ELIGIBILITY CRITERIA

Step 1 Initial Registration: HER-2 Testing

1. Disease Related Criteria
    a. Patients must have histologically or cytologically documented adenocarcinoma of the colon or rectum that is metastatic or locally advanced and unresectable.
    b. Mutation results:
        i. All patients must have molecular testing performed in a CLIA certified lab which includes KRAS and NRAS gene and exon 15 of BRAF gene (BRAF V600E mutation). Patients with any known activating mutation in exon 2 [codons 12 and 13], exon 3 [codons 59 and 61] and exon 4 [codons 117 and 146]) of KRAS/NRAS genes and in exon 15 (BRAFV600E mutation) of BRAF gene are not eligible.
2. Prior/Concurrent Therapy Criteria
    a. Patients must not have been treated with any of the following prior to Step 1 Initial Registration:
        i. Cetuximab, or any other monoclonal antibody against EGFR or inhibitor of EGFR.
        ii. HER-2 targeting for treatment of colorectal cancer. Patients who have received prior trastuzumab or pertuzumab for other indications such as prior history of adjuvant or neoadjuvant breast cancer treatment prior to the development of advanced colorectal cancer are eligible.
    b. Patients must not have had history of severe toxicity and intolerance to or hypersensitivity to irinotecan or any other study drug. Patients must not have had a severe infusion-related reaction during any prior therapy with pertuzumab or trastuzumab.
3. Specimen and Data Submission Criteria
    a. Patients must have tumor slides available for submission for HER-2 testing as described in Section 15.1. HER-2 testing must be completed by the central lab prior to Step 2 Randomization. The central lab will perform HER-2 tests in accordance with instructions provided separately.
4. Regulatory Criteria
    a. Patients must be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines. For Step 1 Initial Registration, the appropriate consent form is the Step 1 Consent Form.
    b. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

Step 2 Randomization

Results of HER-2 testing will be available on the SWOG Specimen Tracking Website and sites will be notified by e-mail within 14 calendar days from submission of the tissue specimen to the central lab.

1. Disease Related Criteria
    a. Patients must have HER-2 amplification as determined by central testing (3+ or 2+ by immunohistochemistry and HER-2 gene amplification by in situ hybridization with a ratio of HER-2 gene signals to centromere 17 signals ≥ 2.0).

b. Patients must have measurable disease that is metastatic or locally advanced and unresectable. Imaging used to assess all disease per RECIST 1.1 must have been completed within 28 days prior to Step 2 Randomization. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

2. Prior/Concurrent Therapy Criteria
   a. Patients must have had at least one prior regimen of systemic chemotherapy for metastatic or locally advanced, unresectable disease. Patients must have progressed following the most recent therapy. Prior treatment with irinotecan is allowed. For patients that received adjuvant chemotherapy: Prior treatment for metastatic disease is not required for patient who experienced disease recurrence during or within 6 months of completion of adjuvant chemotherapy. If the patient received one line of adjuvant treatment and had disease recurrence after 6 months of completing chemotherapy, patients will only be eligible after failing one additional line of chemotherapy used to treat the metastatic or locally advanced, unresectable disease. Patients who have received ≥3 lines of systemic chemotherapy for metastatic or locally advanced, unresectable disease are not eligible.
   NOTE: See Section 5.2e for criteria related to treatment for brain metastases.
   b. Patients must have completed prior chemotherapy, immunotherapy, or radiation therapy at least 14 days prior to Step 2 Randomization and all toxicity must be resolved to CTCAE v4.0 Grade 1 (with the exception of CTCAE v4.0 Grade 2 neuropathy) prior to Step 2 Randomization.
3. Clinical/Laboratory Criteria
   a. Brain metastases are allowed if they have been adequately treated with radiotherapy or surgery and stable for at least 30 days prior to Step 2 Randomization. Eligible patients must be neurologically asymptomatic and without corticosteroid treatment for at least 7 days prior to Step 2 Randomization.
   b. Patients must have a Zubrod Performance Status of 0 or 1. (See Section 10.4)
   c. Patients must be ≥ 18 years of age.
   d. Patients must have a complete physical examination and medical history within 28 days prior to Step 2 Randomization.
   e. Patients must have adequate hematologic function as evidenced by all of the following within 14 days prior to Step 2 Randomization: ANC ≥ 1,500/mcL; platelets ≥ 75,000/mcL; and hemoglobin ≥ 9 g/dL.
   f. Patients must have adequate hepatic function as evidenced by all of the following within 14 days prior to Step 2 Randomization: AST and ALT both ≤ 5 x institutional upper limit of normal (IULN); bilirubin ≤ 1.5 mg/dL.
   g. Patients must have adequate kidney function as evidenced by calculated creatinine clearance > 30 ml/min within 14 days prior to Step 2 Randomization.
      i. Calculated creatinine clearance = (140 - age) x wt (kg) x 0.85 (if female)
      72 x creatinine (mg/dl)
   h. Patients who have had an echocardiogram performed within 6 months prior to Step 2 Randomization, must have ventricular ejection fraction (LVEF) ≥ 50% or ≥ within normal limits for the institution.
   i. Patients must have magnesium, potassium, calcium, sodium, bicarbonate, and chloride performed within 14 days prior to Step 2 Randomization. Results of these tests do not determine eligibility, but the tests are required to establish baseline values. Additional timepoints are noted in Section 9.0.
   j. Patients must not have an uncontrolled intercurrent illness including, but not limited to diabetes, hypertension, severe infection, severe malnutrition, unstable angina, Class III-IV New York Heart Association (NYHA) congestive heart failure (see Section 18.1), ventricular

arrhythmias, active ischemic heart disease, or myocardial infarction within 6 months prior to Step 2 Randomization.

k. Patients must not have any known previous or concurrent condition suggesting susceptibility to hypersensitivity or allergic reactions, including, but not limited to: known hypersensitivity to any of the study treatments or to excipients of recombinant human or humanized antibodies. Patients with mild or seasonal allergies may be included after discussion with the Study Chairs.

l. Patients must not be planning treatment with other systemic anti-cancer agents (e.g., chemotherapy, hormonal therapy, immunotherapy) or other treatments not part of protocol-specified anti-cancer therapy including concurrent investigational agents of any type.

m. No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, ductal carcinoma in situ, other low grade lesions such as incidental appendix carcinoid, or any other cancer from which the patient has been disease and treatment free for two years. Prostate cancer patients on active surveillance are eligible.

n. Patients must not be pregnant or nursing due to risk of fetal or nursing infant harm. Females of child-bearing potential must have a negative serum pregnancy test within 7 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method while on study and for at least 7 months after the last dose of study treatment. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

4. Specimen Submission Criteria
    a. Patients must be given the opportunity to consent to the optional submission of tissue and blood for future research as outlined in Section 15.2.
5. Regulatory Criteria
    a. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines. The appropriate consent form for this registration is the Step 2 Consent Form.
    b. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

Step 3 Crossover Registration (Optional)

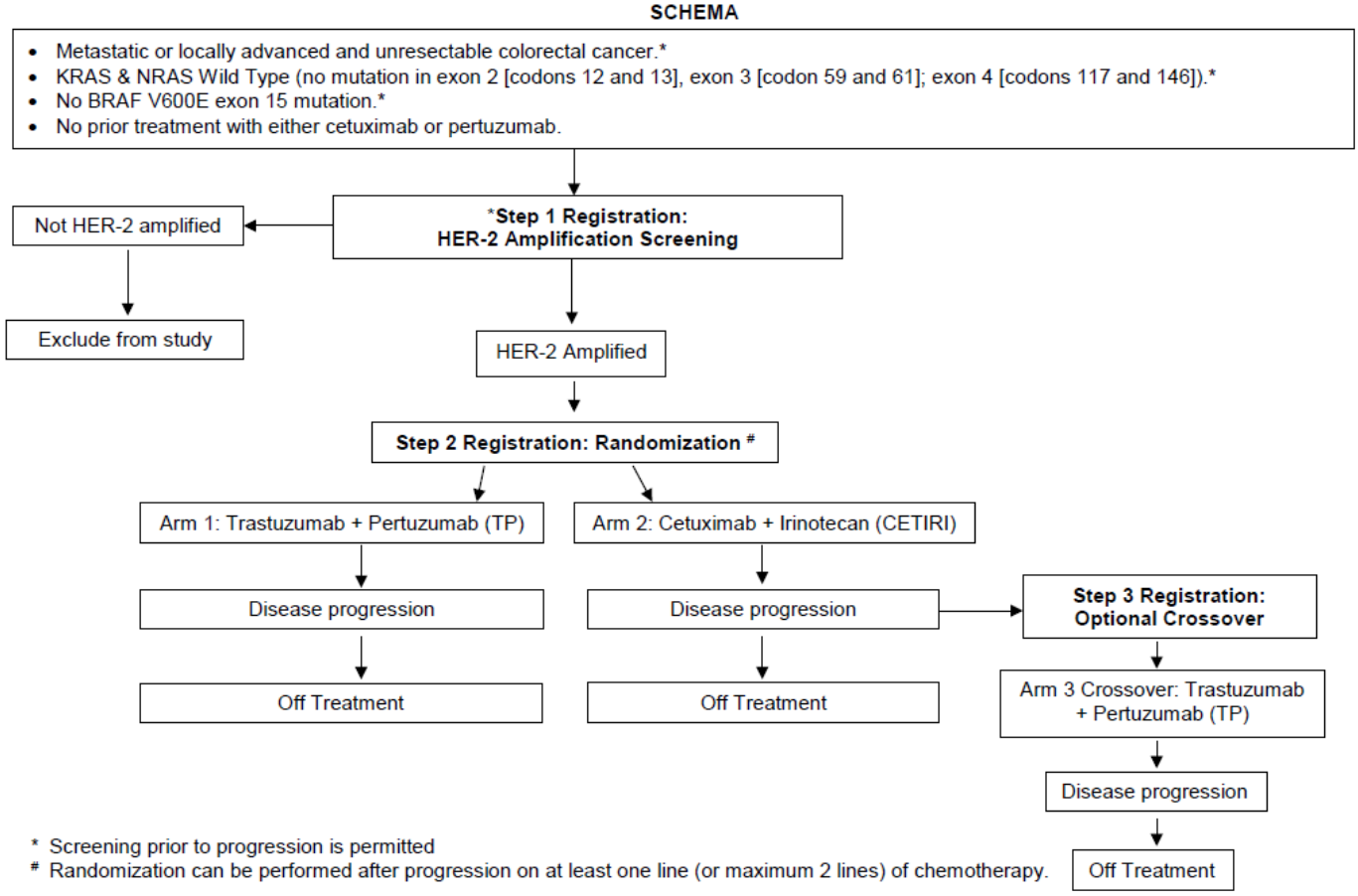
1. Clinical/Laboratory Criteria
    a. Patients must have documented disease progression as defined in Section 10.2d while on CETIRI (Arm 2) on this protocol. The Follow-up Tumor Assessment Form documenting disease progression must be submitted to SWOG prior to Step 3 Crossover Registration. Registration to Step 3 Crossover must be within 28 days of discontinuation of CETIRI protocol treatment. Patients going off treatment for any other reason are not eligible.
    b. Patients must have a Zubrod Performance Status of 0 or 1. (See Section 10.4)
    c. Patients must have adequate hematologic function as evidenced by all of the following within 14 days prior to Step 3 Crossover Registration: ANC ≥ 1,500/mcL; platelets ≥ 75,000/mcL; and hemoglobin ≥ 9 g/dL.

d. Patients must have adequate hepatic function as evidenced by all of the following within 14 days prior to Step 3 Crossover Registration: AST and ALT both ≤ 5 x institutional upper limit of normal (IULN); bilirubin ≤ 1.5 mg/dL.
e. Patients must have adequate kidney function as evidenced by calculated creatinine clearance > 30 ml/min within 14 days prior to Step 3 Crossover Registration.
Calculated creatinine clearance = (140 - age) x wt (kg) x 0.85 (if female)
72 x creatinine (mg/dl)
f. Patients must have left ventricular ejection fraction (LVEF) ≥ 50% or ≥ lower limit of normal for the institution by echocardiogram within 14 days prior to Step 3 Crossover Registration.
g. Patients must have a magnesium, potassium, calcium, sodium, bicarbonate, and chloride performed within 14 days prior to Step 3 Crossover Registration. Additional timepoints are noted in Section 9.0.

2. Regulatory Criteria
a. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines. The appropriate consent form for this registration is the Step 2 Consent Form.
b. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

SCHEMA

- Metastatic or locally advanced and unresectable colorectal cancer.*
- KRAS & NRAS Wild Type (no mutation in exon 2 [codons 12 and 13], exon 3 [codon 59 and 61]; exon 4 [codons 117 and 146]).*
- No BRAF V600E exon 15 mutation.*
- No prior treatment with either cetuximab or pertuzumab.



* Screening prior to progression is permitted
\# Randomization can be performed after progression on at least one line (or maximum 2 lines) of chemotherapy.