Protocol Title: S1613: 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

Target Population: Advanced / Metastatic Colorectal Cancer with HER-2 Amplification

Summary: This randomized phase II trial studies how well Trastuzumab and Pertuzumab work compared to Cetuximab and Irinotecan hydrochloride in treating patients with HER2/neu amplified Advanced / Metastatic Colorectal Cancer that cannot be removed by surgery.

STEP 1 INITIAL REGISTRATION: HER2 TESTING:
- Must have histologically or cytologically documented Adenocarcinoma of the Colon or Rectum that is metastatic or locally advanced and unresectable.
- Must have molecular testing performed in a CLIA-certified lab, with mutations in 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.
- Must not have been treated with any of the following prior to step 1 initial registration:
  - Cetuximab, Panitumumab, or other monoclonal antibody against EGFR or inhibitor of EGFR
  - HER-2 targeting for treatment of Colorectal Cancer
- Must not have history of severe toxicity and intolerance to or hypersensitivity to Irinotecan or any study drug.
- Must have tumor slides available for submission for HER-2 testing.

STEP 2 RANDOMIZATION:
- Must have HER-2 amplification as determined by central testing (3+ or 2+ by IHC and HER-2 gene amplification by ISH with a ratio of HER-2 gene signals to centromere 17 signals ≥ 2.0).
- Must have measurable disease that is metastatic or locally advanced and unresectable.
- Must have had ≥ 1 prior regimen of systemic chemotherapy for 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.
- 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.
- Patients who have had an echocardiogram performed within 6 Months prior to step 2 randomization must have LVEF ≥ 50% or ≥ within normal limits for the institution.
- 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.

STEP 3 CROSSOVER REGISTRATION (OPTIONAL):
- Must have documented disease progression while on CETIRI (Arm 2) on this protocol.
- Registration to step 3 crossover must be within 28 Days of discontinuation of CETIRI protocol treatment.

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For additional information: https://clinicaltrials.gov/ct2/show/NCT03365882