CALGB-80405

A Phase III Trial of Irinotecan / 5-FU / Leucovorin or Oxaliplatin / 5-FU/ Leucovorin With Bevacizumab, or Cetuximab (C225), or With the Combination of Bevacizumab and Cetuximab for Patients With Untreated Metastatic Adenocarcinoma of the Colon or Rectum

ClinicalTrial.gov Identifier: NCT00265850

Study Background

Trial Description

PURPOSE: This randomized phase III trial is studying cetuximab and/or bevacizumab when given together with combination chemotherapy to compare how well they work in treating patients with metastatic colorectal cancer. RATIONALE: Monoclonal antibodies, such as cetuximab and bevacizumab, can block tumor growth in different ways. Some block the ability of tumor cells to grow and spread. Others find tumor cells and help kill them or carry tumor-killing substances to them. Cetuximab may also stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Bevacizumab may also stop the growth of tumor cells by blocking blood flow to the tumor. Drugs used in chemotherapy, such as fluorouracil, leucovorin, oxaliplatin, and irinotecan, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Giving monoclonal antibodies together with combination chemotherapy may kill more tumor cells. It is not yet known whether combination chemotherapy is more effective with cetuximab and/or bevacizumab in treating patients with colorectal cancer.

Arms:

Arm A: FOLFOX or FOLFIRI + bevacizumab: (Active Comparator): Patients receive bevacizumab 5 mg/kg IV every two weeks and then receive either FOLFOX or FOLFIRI every two weeks as described in the intervention section. One cycle is defined as 8 weeks of treatment. Treatment continues until disease progression, unacceptable toxicity or surgery with curative intent as planned.

Arm B: FOLFOX or FOLFIRI + cetuximab: (Experimental): Patients receive cetuximab 400mg/m^2 IV over 2 hours on the first day of treatment, then 250 mg/m^2 IV over 1 hour weekly thereafter. Patients also receive either FOLFOX or

FOLFIRI every two weeks as described in the intervention section. One cycle is defined as 8 weeks of treatment. Treatment continues until disease progression, unacceptable toxicity or surgery with curative intent as planned.

Arm C: FOLFOX or FOLFIRI + cetuximab + bevacizumab: (Experimental): Patients receive cetuximab 400mg/m^2 IV over 2 hours on the first day of treatment, then 250 mg/m^2 IV over 1 hour weekly thereafter. Also, patients receive bevacizumab 5 mg/kg IV every two weeks and then receive either FOLFOX or FOLFIRI every two weeks as described in the intervention section. One cycle is defined as 8 weeks of treatment. Treatment continues until disease progression, unacceptable toxicity or surgery with curative intent as planned.

Objectives:

- OUTLINE: This is a randomized, open-label, multicenter study. Patients are stratified according to physician-selected chemotherapy (FOLFOX or FOLFIRI), prior adjuvant chemotherapy (yes vs no), and prior pelvic radiotherapy (yes vs no). Patients were randomized to 1 of 3 treatment arms.

- Primary Objective:
  - To determine if the addition of cetuximab to FOLFIRI or FOLFOX chemotherapy prolongs survival compared to FOLFIRI or FOLFOX with bevacizumab in patients with untreated, advanced or metastatic colorectal cancer who have K-ras wild type tumors.
- Secondary Objectives:
  - To evaluate response, progression-free survival (PFS), time to treatment failure (TTF), and duration of response (DR) among patients with unresectable advanced metastatic colon cancer treated with bevacizumab or cetuximab in addition to chemotherapy with FOLFIRI or FOLFOX
  - To evaluate toxicity and, in particular, 60-day mortality among patients with unresectable advanced metastatic colon cancer treated with bevacizumab or cetuximab in addition to chemotherapy with FOLFIRI or FOLFOX
  - To describe patients with unresectable locally advanced or metastatic colorectal cancer rendered "resectable" with chemotherapy
- There are premedication guidelines that were established for patients assigned to receive cetuximab. All patients must be premedicated with diphenhydramine hydrochloride 50 mg (or a similar agent) IV prior to the first dose of cetuximab in an effort to prevent an infusion or hypersensitivity reaction. Premedication is also recommended prior to subsequent doses, but at the investigator's discretion the dose of diphenhydramine (or a similar agent) may be reduced. Pretreatment with acetaminophen may also be used.
- There are bevacizumab administration instructions for patients for whom surgery is being contemplated or required. For patients for whom elective surgery is contemplated, bevacizumab is to be discontinued for at least 8 weeks prior to surgery. Bevacizumab may be resumed after at least 4 weeks following surgery. Patients who undergo complete resection of metastatic disease will discontinue protocol therapy

and may receive further treatment at the treating physician's discretion. For patients for whom non-elective surgery is required, hold bevacizumab as long as possible prior to surgery and for at least 6 weeks following surgery.

- Patients received a minimum of two cycles of therapy. Patients were allowed to receive ancillary therapy per protocol. Treatment continued until disease progression, unacceptable toxicity, or surgery with curative intent as planned. After completion of study treatment, patients are followed up to 5 years.

Study Milestones:

Start date: November 2005

Primary Completion Date: February 2015

Publication Information:

Analysis Type: Primary

Pubmed ID: 28632865

Citation: JAMA. 2017 Jun 20;317(23):2392-2401. doi: 10.1001/jama.2017.7105.

Associated Datasets: NCT00265850-D1-Dataset.csv (consorttable), NCT00265850-D2-Dataset.csv (figure2), NCT00265850-D3-Dataset.csv (outcometext_supplemental), NCT00265850-D4-Dataset.csv (supplemental_etable2), NCT00265850-D5-Dataset.csv (table1), NCT00265850-D6-Dataset.csv (table2), NCT00265850-D7-Dataset.csv (grade5), NCT00265850-D8-Dataset.csv (supplemental_modreasons)

Dataset Information:

Dataset Name: NCT00265850-D6-Dataset.csv (table2)

Description: Dataset NCT00265850-D6-Dataset.csv (table2) is one of 8 datasets associated with PubMed ID 28632865. This dataset contains information that will allow you to reproduce table 2 of the manuscript.

There is a flag in Dataset NCT00265850-D1-Datases.csv (consorttable) contains a flag indicating the number of patients evaluable for adverse events.

NCT00265850-D6-Dataset.csv (table2) Data Dictionary:

LABEL	NAME	elements	comments
Toxicity	tox	Fatigue, Sensory Neuropathy, Diarrhea, Blood or Bone Marrow	
Patient ID	patid		
AE Grade	GRADE	4, 3	NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
AE Relation	REL_SMED	4, 5, 3	3=possibly related to treatment, 4=Probably related to treatment, 5=definitely related to treatment
Treatment Arm	TREAT_ASSIGNED	Chemo + Bev, Chemo + Cetux	