C80405

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: Secondary

Pubmed ID: 31042420

Citation: J Clin Oncol. 2019 Aug 1;37(22):1876-1885. doi: 10.1200/JCO.18.02258. Epub 2019 May 1.

Publication Title:

Impact of Consensus Molecular Subtype on Survival in Patients With Metastatic Colorectal Cancer: Results From CALGB/SWOG 80405 (Alliance)

Objective:

To determine the predictive and prognostic value of the consensus molecular subtypes (CMSs) of colorectal cancer (CRC) that represent a merging of gene expression–based features largely in primary tumors from six independent classification systems and provide a framework for capturing the intrinsic heterogeneity of CRC in patients enrolled in CALGB/SWOG 80405.

Associated Datasets:

NCT00265850-D14-Dataset.csv (consort),

NCT00265850-D15-Dataset.csv (nctn_cms)

Dataset Information:

Dataset Name: NCT00265850-D15-Dataset.csv (nctn_cms)

Description: Dataset NCT00265850-D15-Dataset.csv (nctn_cms) is one of 2 datasets associated with PubMed ID 31042420, a non-primary publication for trial C80405. This dataset contains the data to determine the predictive and prognostic value of the consensus molecular subtypes (CMSs) of colorectal cancer (CRC).

Data from this trial's primary publication can be found in NCT00265850-D1 through -D8.

Data can be used to approximate published study findings, but exact reproduction of previous manuscripts may not be possible in some cases (e.g., when data must be modified for de-identification purposes or have undergone further data cleaning).

Data in this dataset has slight discrepancies from those found in Table 1, due to subsequent data cleaning and querying missing data.

NCT00265850-D15-Dataset.csv (nctn_cms) Data Dictionary:

LABEL	NAME	ELEMENTS	COMMENTS
Patient ID	PATID		
Primary Cohort Patient	primary	Yes	
Arm	TREAT_ASSIGNED	Bevacizumab, Cetuximab	
PFS Status	pf_stat	Event, Censor	
Progression-Free Survival Months	pf_months		
Overall Survival Status	dead	Event, Censor	
Overall Survival Months	fu_months		
CMS	CMS	CMS2, CMS4, CMS1, CMS3	Missing indicates patient was not part of the CMS analysis populations
CMS Population	cms_pop	1= patient is part of the CMS population, 0 = patient is not part of the CMS population	Flag variable to obtain CMS population
Age (years)	age		
Protocol Chemotherapy (FOLFOX/FOLFIRI)	prot_chemo	FOLFOX, FOLFIRI	

Prior Adjuvant Chemotherapy	pr_adj	No, Yes	
Prior Pelvic Radiation	pr_rad	No, Yes	
Gender	SEX_ID	Female, Male	
Race	race	White, Other	Missing indicates data was not collected
ECOG PS	PERFORMANCE_ID	0, 1, 2	
Number of Metastatic Sites	met_grp	3+, 1, 2	Missing indicates data was not collected
Intent of Treatment	TXINTENT	Palliative, Curative Intent, Missing	
Tumor Location	sidedness	Left, Right/Transverse	Missing indicates the data was not collected. This variable has 2 levels: Left or Right/transverse.
Tumor Location	side3	Left, Right, Transverse	This variable has 3 levels: Left or Right or Transverse. Missing indicates data was not collected.
Liver Metastases Only	liver_only	No, Yes	Missing indicates data was not determined and/or collected.
In Place Primary	primary_inplace	No, Yes	
Disease Diagnosis	synch_v_meta	Synchronous, Metachronous	Missing indicates data not collected.
KRAS Signature (Nanostring)	kras_like_mut	Mutant, Wildtype	Missing indicates data not collected.
KRAS	KRAS_mut	Wildtype, Mutant	Missing indicates data not collected.
BRAF Signature (Nanostring)	braf_like_mut	Wildtype, Mutant	Missing indicates data not collected.
BRAF	BRAF_mut	Wildtype, Mutant	Missing indicates data not collected.
BRAF (Signature or Genentech)	any_braf	Wildtype, Mutant	Missing indicates data not collected.
MSI Signature (Nanostring)	msi_h_like	MSI-S, MSI-H	Missing indicates data not collected.

MSI Status (Genentech)	MSI_Status	MSS, MSI-L, MSI-H	Missing indicates data not collected.
MSI Status (Signature or Genentech)	msi	MSS, MSI-H	Missing indicates data not collected.