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: 30865548

Citation: J Clin Oncol. 2019 May 10;37(14):1217-1227. doi: 10.1200/JCO.18.01798. Epub 2019 Mar 13.

Publication Title:

Mutational Analysis of Patients With Colorectal Cancer in CALGB/SWOG 80405 Identifies New Roles of Microsatellite Instability and Tumor Mutational Burden for Patient Outcome.

Publication Objective:

This study aimed to determine the tumor mutational profile of patients with mCRC in CALGB/SWOG 80405, to evaluate the prognostic value of DNA mutations, and to determine the differential treatment effects of bevacizumab versus cetuximab in patients with a specific mutational profile. Associated Datasets:

NCT00265850-D9-Dataset.csv (consort_braf),

NCT00265850-D10-Dataset.csv (consort_msi),

NCT00265850-D11-Dataset.csv (consort_mut_load),

NCT00265850-D12-Dataset.csv (consort_ras),

NCT00265850-D13-Dataset.csv (nctn_pcr)

Dataset Information:

Dataset Name: NCT00265850-D13-Dataset.csv (nctn_pcr)

Description: Dataset NCT00265850-D13-Dataset.csv (nctn_pcr) is one of 5 datasets associated with PubMed ID 30865548. This dataset contains data on the clinical characteristics, demographics, and endpoint analyses.

For the 12 biomarker point mutation variables, missing values indicate that PCR testing was not performed for this patient. Otherwise, for clinical variables, missing values indicate that the data was not collected for this patient.

This data submission, NCT00265850-D13-Dataset.csv, contains the data used to generate the results in PubMed ID 30865548, a non-primary publication from trial C80405. Data from this trial's primary publication can be found in datasets NCT00265850-D1-Dataset.csv through NCT00265850-D8-Dataset.csv. Data that are identical to those presented in these available datasets are not duplicated in this submission.

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).

'MND' as noted in the dictionary definition indicates Mutation Not Detected.

NCT00265850-D13-Dataset.csv (nctn_pcr) Data Dictionary:

LABEL	NAME	ELEMENTS	COMMENTS
Patient ID	patid		
Mutational Analysis Population	main_pop	1=patient included in mutation analysis population, 0=patient not included in mutational analysis population	
Arm	TREAT_ASSIGNED	Bev+Cet, Bevacizumab, Cetuximab	
Primary Cohort Patient	primary	No, Yes	
Overall Survival (months)	fu_months		
Overall Survival Status	dead	Event, Censor	
Progression-Free Survival (months)	pf_months		
PFS Status	pf_stat	Event, Censor	
Protocol Chemo	prot_chemo	FOLFOX, FOLFIRI	

Prior Adjuvant Chemotherapy	pr_adj	No, Yes	
Prior Pelvic Radiation	pr_rad	No, Yes	
Gender	SEX_ID	Male, Female	
Age (years)	age		
Tumor Biology	synch_v_meta	Synchronous, Metachronous	
Race (labelled incorrectly as ethnicity in manuscript)	RACE_ID	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, Not Reported Unknown, White	Missing indicates the data was not collected.
ECOG PS	PERFORMANCE_ID	0, 1, 2	
Number of Metastatic Sites	met_grp	1, 3, 2	
Tumor Location	side	Right, Left, Unknown, Transverse, Multiple	
Liver Metastases Only	liver_only	Yes, No	
	AKT	MND, NO CALL	
	APC	MND, APC_Q1367X, APC_R564X, APC_R302X, APC_R1450X, APC_R876X, APC_R213X, APC_Q1367X/R1450X, APC_R564X/Q1367X, APC_R876X/R1450X, APC_R213X/R1450X	
	BRAF	MND, BR_V600E, BR_V600M, BR_K601E	
	CTNNB1	MND, NO CALL, CTNNB1_T41A, CTNNB1_S45F	
	EGFR	MND, NO CALL, EG_R671C, EG_S768T	
	FBXW7	MND, NO CALL, FBXW7_R465H, FBXW7_R505C, FBXW7_R367X,	

		FBXW7_S582L, FBXW7_R479Q, FBXW7_R465C	
	HRAS	MND, NO CALL	
	KRAS	KR_A146T, KR_A146V, KR_G12A, KR_G12C, KR_G12C/Q61R, KR_G12D, KR_G12F, KR_G12R, KR_G12S, KR_G12S/Q61K, KR_G12V, KR_G13C, KR_G13D, KR_G13R, KR_G13S, KR_G13S/Q61HC, KR_K117N, KR_L19F, KR_Q22K, KR_Q61HC, MND, NO CALL	
	MET	MND, NO CALL, ME_T1010I, ME_N375S	
	NRAS	MND, NR_Q61K, NR_Q61R, NR_G13X, NR_G12X	
	PIK3CA	PK_H1047X, MND, NO CALL, PK_E545X, PK_E542K,	

		PK_R88Q, PK_Y1021C, PK_N345K, PK_C420R, PK_K111N/C420R, PK_M1043I, PK_E542K/H1047X, PK_R108H/C420R, PK_Q546X, PK_R38C, PK_K111E, PK_G1049R	
	TP53	TP53_R273H, MND, TP53_R248W, TP53_R282W, TP53_R213X, TP53_R175H, TP53_R248Q, TP53_R196X, TP53_R273C, TP53_G245S, TP53_R196X/R282W, TP53_R175H/R248W, TP53_C176F, TP53_R213X/R282W, TP53_R248Q/R273C, TP53_R273H/R282W, TP53_R248W/R282W, TP53_R248Q/R273H	
BRAF Mutation Status	BRAF_mut	Wildtype, Mutant	Missing means PCR testing was not performed or no BRAF call could be made.
KRAS Mutation Status	KRAS_mut	Wildtype, Mutant	Missing means PCR testing was not performed or no KRAS call could be made.
NRAS Mutation Status	NRAS_mut	Wildtype, Mutant	Missing means PCR testing was

			not performed or no NRAS call could be made.
PIK3CA Mutation Status	PIK3CA_mut	Mutant, Wildtype	Missing means PCR testing was not performed or no PIK3CA call could be made.
Triple Negative (NRAS/KRAS/BRAF)	triple_neg	All Wildtype, Any Mutation	A patient is classified as "Any Mutation" if they have a mutation in EITHER NRAS, KRAS, or BRAF. A patient is classified as "All Wildtype" if they are Wildtype in ALL three. A missing value indicates that neither of the above criteria could be met.
Quadruple Negative (NRAS/KRAS/BRAF/PIK3CA)	quadruple_neg	Any Mutation, All Wildtype	A patient is classified as "Any Mutation" if they have a

			mutation in EITHER NRAS, KRAS, BRAF, or PIK3CA. A patient is classified as "All Wildtype" if they are Wildtype in ALL four. A missing value indicates that neither of the above criteria could be met.
RAS Mutation Status	expanded_mut	Wildtype, Mutant	A patient is classified as "Mutant" if they are EITHER KRAS Mutant or NRAS Mutant. A patient is classified as "Wildtype" if they are BOTH KRAS Wildtype and NRAS Wildtype. A missing values indicates that neither of the above

			criteria could be met.
MSI Status	msi_both	MSS, MSI-H	
Tumor Molecular Burden	mut_load		This is defined as the number of mutations divided by the Mb of the genomic region being sequenced.
Tumor Molecular Burden	mut_load_grp	>8, <=8	>8 was considered high burden and <=8 was considered low.
Tumor Molecular Burden (4 Levels)	mut_load4	9+, 5 to 6, 0 to 4, 7 to 8	