N0147:

A randomized phase III trial of oxaliplatin (OXAL) plus 5-Fluorouracil (5-FU)/leucovorin (CF) with or without cetuximab (C225) after curative resection for patients with stage III colon cancer

ClinicalTrials.gov Identifier: NCT00079274

Study Background

Trial Design: This randomized phase III trial was originally designed to compare three different combination chemotherapy regimens to see how well they work. As of September 1, 2004, the study was expanded to a total of 6 arms (the original 3 arms (A, B, C) and 3 additional arms which were the same as the first 3 but with cetuximab) in treating patients who have undergone surgery for stage III colon cancer. Drugs used in chemotherapy, such as irinotecan hydrochloride, fluorouracil, leucovorin calcium, and oxaliplatin, work in different ways to stop tumor cells from dividing so they stop growing or die. Monoclonal antibodies such as cetuximab can locate tumor cells and either kill them or deliver tumor-killing substances to them without harming normal cells. Combining more than one chemotherapy drug with monoclonal antibody therapy and giving them after surgery may kill any remaining tumor cells. It was not known at the time this study was developed which combination chemotherapy regimen is more effective after surgery in treating colon cancer. This study had several key changes, based on the results of other phase III trials. As of 6/1/2005, patients no longer received irinotecan on this study and treatment arms B, C, E, and F were discontinued. Patients on arms B and C crossed to arm A. Patients on arms E and F crossed to arm D. Patients on arms C and F who had not gotten to irinotecan continued on arms A and D, respectively. As of 8/18/2008, pre-screening for Kirsten rat sarcoma (KRAS) status was added with mutant KRAS (or KRAS not evaluable) patients put on arm G and wild-type KRAS patients randomized between arm A and arm D. Patients on arm G were treated per physician discretion and followed for disease and survival status. KRAS was determined in a central laboratory and was process for all patients on this study. The primary endpoint of this study was modified on 8/18/2008 to focus on patients having wild-type KRAS tumors. All modifications were approved by the Central Institution Review Board, local Institutional Review Boards, NCI, and the NCCTG Data Safety Monitoring Board.Arm I (Saltz regimen): Patients receive irinotecan IV over

90 minutes followed by leucovorin calcium IV over 15 minutes and fluorouracil IV once a week for 4 weeks followed by 2 weeks of rest. Courses repeat every 6 weeks. (Arm I closed to accrual as of March 15, 2002.)

- ARM A: Patients receive oxaliplatin intravenously (IV) over 2 hours, leucovorin calcium IV over 2 hours, and fluorouracil IV continuously over 46-48 hours on days 1. Treatment repeats every 14 days for up to 12 courses in the absence of unacceptable toxicity or recurrent disease.
- ARM B (closed to accrual as of 6/1/2005--currently enrolled patients may cross over to arm I for remainder of therapy): Patients receive irinotecan hydrochloride IV over 2 hours on day 1 and leucovorin calcium and fluorouracil as in arm A. Treatment repeats every 14 days for up to 12 courses in the absence of unacceptable toxicity or recurrent disease.
- ARM C (closed to accrual as of 6/1/2005--currently enrolled patients may cross over to arm I for remainder of therapy): Patients receive the same treatment as in arm A for 6 courses followed by the same treatment as in arm B for 6 courses (total of 12 courses). Treatment continues in the absence of unacceptable toxicity or recurrent disease.
- ARM D: Patients receive cetuximab* IV over 1 hour on days 1 and 8 and oxaliplatin, leucovorin calcium, and fluorouracil as in arm A. Treatment repeats every 14 days for up to 12 courses in the absence of unacceptable toxicity or recurrent disease.
- ARM E (closed to accrual as of 6/1/2005--currently enrolled patients may cross over to arm D for remainder of therapy): Patients receive cetuximab* as in arm D and irinotecan hydrochloride, leucovorin calcium, and fluorouracil as in arm B. Treatment repeats every 14 days for up to 12 courses in the absence of unacceptable toxicity or recurrent disease.
- ARM F (closed to accrual as of 6/1/2005--currently enrolled patients may cross over to arm D for remainder of therapy): Patients receive cetuximab* as in arm D and chemotherapy as in arm C.
- ARM G (added as of 8/18/2008, mutant KRAS (or KRAS not evaluable) patients): Locally directed therapy.
- ARM I (Saltz regimen): Patients receive irinotecan IV 90 minutes followed by leucovorin calcium IV over 15 minutes and fluorouracil IV once a week for 4 weeks followed by 2 weeks of rest. Courses repeat every 6 weeks. (Arm I closed to accrual as of March 15, 2002.)

NOTE: *Cetuximab is administered over 2 hours at a higher dose on day 1 of course 1 only.

Quality of life (QOL) is assessed at baseline, 3 months, and at the end of

therapy. As of 8/18/2008, QOL was discontinued.

Patients are followed for a maximum of 8 years from randomization.

Objectives:

Primary:

- To compare the disease-free survival (DFS) in patients with stage III (TxN1-2M0) colon cancer who are KRAS wild-type randomized to 24 weeks of adjuvant chemotherapy with either: (1) Oxaliplatin (OXAL) + 5-fluorouracil/leucovorin (5-FU/LV) (FOLFOX) or (2) FOLFOX + C225.

Secondary:

1. To compare the DFS in unselected patients with stage III (TxN1-2M0) colon cancer randomized to 24 weeks of adjuvant chemotherapy with either: (1) Oxaliplatin (OXAL) + 5-fluorouracil/leucovorin (5-FU/LV) (FOLFOX) or (2) FOLFOX + C225.
2. To compare the overall survival (OS) in patients with KRAS wildtype tumors, and in unselected patients with stage III (Tx, N1-2, M0) colon cancer randomized to 24 weeks of adjuvant chemotherapy with FOLFOX with or without C225.
3. To assess toxicities resulting from the addition of C225 to chemotherapy.
4. To compare the quality of life, measures of patient satisfaction, nutrition, and cancer risk in patients treated with FOLFOX with or without C225, using four patient-completed questionnaires.

Stratification Factors:

- Positive lymph node involvement: 1-3 vs. ≥ 4.
- Histology: High (poorly differentiated or undifferentiated) vs. low (well or moderately differentiated).
- Clinical T Stage: (T1 or T2) vs. T3 vs. T4.

Study History:

2/10/2004	Activation Date
11/25/2009	Close Date
11/25/2012	Primary Completion Date
02/08/2015	Study Completion Date

Publication Information

Analysis Type:	Primary Endpoint Analysis
PubMed ID:	22474202
Citation:	Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, Smyrk TC, Sinicrope FA, Chan E, Gill S, Kahlenberg MS, Shields AF, Quesenberry JT, Webb TA, Farr GH, Pockaj BA, Grothey A, Goldberg RM. Effect of Oxaliplatin, Fluorouracil, and Leucovorin With or Without Cetuximab on Survival Among Patients With Resected Stage III Colon CancerA Randomized Trial. *JAMA.* 2012;307(13):1383-1393. doi:10.1001/jama.2012.385
Associated Datasets:	NCT00079274-D1-Dataset (char) NCT00079274-D2-Dataset (obj) NCT00079274-D3-Dataset (tox)

Dataset Information

Dataset Name: NCT00079274-D1-Dataset (char)

Description: The NCT00079274-D1-Dataset.csv dataset is one of 3 datasets associated with PubMed ID 22474202. This dataset contains information on baseline characteristics, eligibility, and follow-up status for patients on arms A and D only. Note: BRAF information is not included in this upload.

NCT00079274-D1-Dataset.csv (char) Data Dictionary

Variable Description	Variable Name	Code	Notes
Unique identifier for each patient	patref		
Adherence	adherenc	1=Yes 2=No	
Age category:	agecat	< 40, 40-69, >=70	
Experimental arm:	arm	A: (FOLFOX) Oxaliplatin + 5-fluorouracil/Leucovorin Regimen (KRAS wildtype) D: FOLFOX + Cetuximab (KRAS wildtype)	
BMI	bmi2	Numeric	If missing, height and/or weight were not recorded at baseline.
Bowel obstruction :	bwl_obs	1=Yes 2=No	
Bowel perforation:	bwl_perf	1=Yes 2=No	Publication has a display issue, arm D, mutated, and no perforation should display 323 corresponding with 94%.
Days from randomization until last protocol therapy was given	endat_time	Numeric	If missing, no protocol therapy was given or patient has not ended treatment at time of publication.
Reason Treatment Ended:	endatrsn	1 = Treatment completed per protocol criteria 2 = Refused further therapy 3 = Adverse Event/Side Effects/Complications 4 = Disease Progression, relapse during active treatment	If missing, no end of treatment reason was recorded at time of publication.

		5 = Alternative therapy 6 = Other Medical Problems 7 = Death on Study 8 = Other 10 = Disease progression before active treatment 11 = Cytogenetic Resistance 12 = Refused further treatment before beginning protocol therapy	
Patient Status	excluded	9=Ineligible 8=Major Protocol Violation 7=Cancel (withdrew prior to starting therapy) Missing = no major issue	Patients were not excluded from analysis. This helps show the progress/status of the patient. (Intent to treat trial)
Histology:	histo_g	1=High (poorly differentiated or undifferentiated) 2=Low (well or moderately differentiated)	
Patient was lost to follow up:	lost2fup	y = Yes Missing = No	
Positive lymph node involvement:	nodes	1 = 1-3 2 = >=4	
Total Number of Cycles Given	numcycle		If missing, total cycles was not yet assessed at the time of the publication.
Response status at the most recent assessment (on treatment):	obj_stat	0=NED 6=Recurrence 8=Not evaluated	If missing, patient did not have a response assessment reported at time of publication. They were not used in the analysis.
ECOG Performance Status:	ps	0 = 0 1 = 1 2 = 2+	If missing, baseline PS was not recorded.
Race:	racecat	b=black w=white oth=other	
Sex:	sex	m=Male f=Female	
Clinical T Stage:	stage_g	1=T1 or T2 2=T3 3=T4	If missing, T-stage was not recorded at baseline.
Biomarker KRAS:	wild	0 = Mutant 1 = Wild-type Missing = indeterminate	The KRAS mutated portion of Table 2 can be obtained when ‘wild’ =0 and by arm only. Observations with missing ‘wild’ are not included