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-D3-Dataset (tox)

Description: The NCT00079274-D3-Dataset.csv dataset is one of 3 datasets associated with PubMed ID 22474202. This dataset contains information on grade 3 or higher reported toxicity for patients on arms A and D only.

All patients on arms A and D who were evaluated for adverse events are included in this dataset. If the patient did not report an adverse event graded 3 or higher, then the grade, tox, and maxgrade are missing.

NCT00079274-D3-Dataset.csv (tox) Data Dictionary

Variable Description	Variable Name	Code	Notes
Unique identifier for each patient	patref		
Treatment Arm	arm	A: (FOLFOX) Oxaliplatin + 5-fluorouracil/Leucovorin Regimen (KRAS wildtype) D: FOLFOX + Cetuximab (KRAS wildtype)	
Severity of the adverse event according to CTCAE v3.0 guidelines	grade		Grading scale determined by CTCAE v3.0 grading scale. Grade 3 or higher only.
Adverse event term according to CTCAE v3.0	tox		Adverse event term according to CTCAE v3.0 and MedDRA 6.0
Maximum severity of an adverse event according to CTCAE v3.0 over all adverse events	maxgrade		Grading scale determined by CTCAE v3.0 grading scale. Grade 3 or higher only. Patients that have a missing grade but have a maxgrade were included in the overall analysis of adverse events. These patients reported a grade three that was not specified in the manuscript.