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Cetuximab combined with induction oxaliplatin and capecitabine, followed by neoadjuvant chemoradiation for locally advanced rectal cancer: SWOG 0713

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Abstract

Background—Neoadjuvant chemoradiation (NCRT) is standard treatment for locally advanced rectal cancer. Pathologic complete response (pCR) has associated with improved survival. In modern phase III trials of NCRT, pCR ranges from 10–20%. Cetuximab improves response in *KRAS* wild-type (*KRAS*-wt) metastatic colorectal cancer. S0713 was designed to assess improvement in pCR with cetuximab added to induction chemotherapy and NCRT for locally advanced, *KRAS*-wt rectal cancer.

Methods—Patient eligibility: stage II-III biopsy-proven, *KRAS*-wt rectal adenocarcinoma; no bowel obstruction; adequate hematologic, hepatic and renal function; performance status of 0–2. Target enrollment: 80 patients. Treatment: induction chemotherapy with weekly capecitabine, oxaliplatin (wCAPOX) and cetuximab followed by the same regimen concurrent with radiation (omitting day 15 oxaliplatin). If fewer than seven pCR were observed at planned interim analysis after 40 patients received all therapy, the study would close. Eighty eligible patients would provide

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90% power given a true pCR rate > 35% at a significance of 0.04. The regimen would lack future interest if pCR probability was 20% or less.

Results—Between February 2009 and April 2013, 83 patients registered. Four were ineligible and four not treated, leaving 75 evaluable for clinical outcomes and toxicity, of which 65 had surgery. Twenty of 75 patients had pCR (27%, 95% CI 17–38%); 19 (25%) had microscopic cancer; 36 (48%) had minor/no response (including 10 without surgery). 3-year DFS was 72% (95% CI 61–81%).

Conclusions—Our trial did not meet the pCR target of 35%. Toxicity was generally acceptable. This regimen cannot be recommended outside of a clinical trial setting.

MicroAbstract

Cetuximab enhances response in *KRAS* wild-type metastatic colorectal cancer. This trial selected patients with *KRAS* wild-type rectal cancer to assess added benefit from cetuximab in the neoadjuvant setting. Complete pathologic response (pCR) was the surrogate for benefit. Eighty patients were enrolled targeting a pCR rate of 35%, an outcome that wasn't achieved. This regimen cannot be recommended for general use.

Keywords

SWOG; phase II; chemotherapy; pCR; *KRAS*

BACKGROUND

With total mesorectal excision (TME) and neoadjuvant chemoradiation as standard therapy, local control for rectal adenocarcinoma has greatly improved compared to historical post-operative chemotherapy and radiation.¹ Unfortunately, distant recurrence remains stable in the 25–35% range.² Adjuvant trial design for rectal cancer derives from colon cancer trials, where addition of oxaliplatin to fluoropyrimidine therapy has provided survival benefit.^{3,4} However, for rectal cancer, oxaliplatin has failed to improve outcomes in most randomized trials testing this hypothesis.^{5,6,7,8,9}

Many patients with residual cancer following neoadjuvant chemoradiation do not receive adjuvant treatment due to prolonged surgical recovery.^{10,11} Administering planned adjuvant chemotherapy in the pre-operative setting might address this.^{12,13}

The neoadjuvant approach allows efficacy evaluation through pathologic response assessment. In many cancers, pCR correlates with improved outcome and is considered a surrogate of therapeutic benefit in signal-seeking phase II trials.^{14,15} Thus, scheduling chemotherapy prior to chemoradiation to increase pCR is reasonable.¹⁶

We designed a trial for locally advanced *KRAS*-wt adenocarcinoma of the rectum. Cetuximab was investigated based upon demonstrated benefit in *KRAS*-wt metastatic colon cancer.^{17,18} At this trial's inception, oxaliplatin was being investigated in neoadjuvant chemoradiation trials for rectal cancer.¹⁹ Additionally, we planned a course of induction

chemotherapy prior to chemoradiation with the hypothesis of enhancing pCR rate through increased chemotherapy exposure.¹

METHODS

The primary objective of this trial was to assess pCR in patients with stage II-III *KRAS*-wt adenocarcinoma of the rectum treated with wCAPOX and cetuximab given as induction therapy followed by the same regimen concurrent with external beam radiotherapy (EBRT) to the pelvis. Secondary objectives included estimation of three-year disease-free survival (DFS) and the frequency and severity of toxicities.

Primary eligibility criteria were biopsy proven, untreated *KRAS*-wt stage II-III rectal cancer with adequate performance status and organ function. Other inclusion and exclusion criteria are listed in the study protocol (supplemental data). Prior to registration, tumor tissue was submitted to a CLIA certified laboratory to confirm *KRAS*-wt status. All patients were evaluated by the medical, surgical and radiation oncologists providing treatment prior to the initiation of therapy. Site institutional review board approval and patient written informed consent was obtained prior to trial enrollment.

The protocol consisted of: cycle 1 induction chemotherapy (days 1–35) followed by a 14 day rest period; cycle 2 chemoradiation (days 50–84); and surgery (Figure 1). Chemotherapy was administered in two 35 day cycles. Oxaliplatin 50 mg/m² was administered on days 1, 8, 15, 22 and 29 of the first cycle and days 1, 8, 22 and 29 of the second cycle. A cetuximab loading dose, 400 mg/m², was administered day 1 followed by 250 mg/m² on days 8, 15, 22, and 29 of cycle 1 and days 1, 8, 15, 22, and 29 of cycle 2. Capecitabine was administered in two 825 mg/m² doses q 12 hours Monday through Friday of all chemotherapy cycles.

EBRT 180 cGy daily, Monday through Friday for 25 fractions, began concurrently with the second chemotherapy cycle. A 540 cGy boost was delivered in three 180 cGy fractions for patients with clinical T3 cancers (total dose 5040 cGy), and 900cGy in five 180 cGy fractions for patients with clinical T4 cancers (total dose 5400 cGy). Central review of the radiation treatment plan was required before initiation of therapy, with a final review occurring after protocol completion.

Surgery was to occur between three and eight weeks of chemoradiation completion. TME principles applied with sphincter preservation as a goal.

The primary statistical endpoint was pCR. The regimen would be considered of further interest if the pCR rate were 35% or greater, and of no further interest if 20% or less. Eighty eligible patients were needed to provide 90% power given a true pCR rate > 35% at a significance of 0.04 based on the SWOG two-stage design.²⁰ Those without surgery were assumed not to have achieved pCR. An interim analysis was planned after response data for the first 40 patients treated became available: 7 or fewer pCRs or failure of 25% or more of this cohort to complete protocol therapy would result in study closure. DFS was estimated by the method of Kaplan and Meier. For toxicity/safety analysis, 80 patients were adequate

to estimate that any toxicity with a 5% occurrence rate was likely (98%) to be seen at least once.

RESULTS

Between February 2009 and April 2013, 83 patients from 20 institutions were registered to this trial. Reasons for ineligibility included: inadequate baseline disease assessment (2), location of disease (1), and distant metastases (1). Four patients who received no protocol therapy were not included in any study analyses.

Seventy-five patients are included in the final analysis, including two patients without documentation of *KRAS*-wt status and one without a baseline radiology report. Eleven patients were removed from protocol therapy before completion of all protocol treatment due to: toxicity- primarily gastrointestinal (7 patients), refusal to undergo chemoradiation, non-compliance, progression, and death (1 patient each).

Demographics for the 75 eligible patients who received therapy are summarized in Table 1.

Sixty-five patients (87%) underwent surgery. Of those that did not undergo surgery, subsequent review showed three of these to have died of disease progression, two to have died of other causes, and five to be without evidence of disease at last follow-up submission, two of whom had non-protocol surgery.

Clinical Results

Twenty patients, 27% (95% confidence interval 17–38%) achieved a pCR at surgery. The protocol specified historical rate of pCR was 20%; a one-sided exact binomial test of the observed pCR rate to the historical rate gave $p = 0.10$. Nineteen additional patients (25%) had microscopic cancer, and 36 patients (48%) were coded non-responders (including minimal or partial responses by trial design). The 3-year disease-free survival was 72% (95% CI 61%–81%) (Figure 2).

Toxicity

Seventy-five patients were included in the adverse event analysis. Dominant side-effects were gastrointestinal, integumentary and neurologic. Hematologic toxicity was rare. Grade 3 events occurring in at least 10% of patients were diarrhea, nausea/vomiting, rash, hypokalemia and lymphopenia. Two patients experienced grade 4 events: dehydration, and colitis with hyponatremia. One death from multi-organ failure with associated grade 4 acidosis, dehydration and diarrhea was considered possibly related to study treatment. Adverse events are listed in Table 2.

DISCUSSION

This single arm phase II trial assessing the addition of cetuximab to wCAPOX and radiation in a selected *KRAS*-wt rectal cancer population failed to meet the primary endpoint of a 35% pCR rate. Patient ineligibility and dropout were higher than anticipated in our trial

resulting in a smaller evaluable cohort. The impact of non-surgical cases on pCR cannot be known.

In results published since our trial began, addition of oxaliplatin to neo-adjuvant 5-fluorouracil based chemoradiation for locally advanced rectal cancer failed to demonstrate added benefit, as assessed by pCR rate, in all but one large randomized trial (CAO/ARO/AIO-04)⁵⁻⁹. In these trials, patients receiving oxaliplatin experienced more frequent and higher grade toxicities. Although oxaliplatin toxicity could potentially have negated cetuximab benefit, several small previously reported phase II trials integrating cetuximab with neoadjuvant capecitabine and radiation demonstrated pCR rates not significantly increased over historical rates with chemoradiation alone.^{21,22,23} Additionally, a pooled analysis of three pre-operative phase I-II trials of radiation and CAPOX, with or without cetuximab, suggested possible negative interaction from cetuximab.²⁴

Previously reported rectal cancer trials have assessed the impact of adding cetuximab to neoadjuvant fluoropyrimidine, oxaliplatin, and radiation in an effort to enhance pCR rate. In one such phase I-II trial not demonstrating an increased pCR signal, the authors suggested the order of treatment administration might impact efficacy²⁵. Recent investigation has shown that radiation can act as a vaccine by release of tumor antigens which induce immune response.²⁶ Possibly, chemoradiation would be more effective if administered first.

Radiosensitization was another rationale for investigating cetuximab.²⁷ Nonetheless, chemoradiation with cetuximab failed to eradicate cancer in 73 of the patients in this trial. Results from this and similar trials adding cetuximab to pre-operative rectal cancer therapy are similar to results with chemoradiation alone, implying little sensitization benefit.

Although pCR has been associated with improved survival, its surrogacy has recently been called into question.^{28,29} pCR does not capture microscopic only disease which in an analysis of tumor regression grading systems has a positive impact on outcome.³⁰

The EXPERT-C trial included 160 patients randomized to CAPOX or CAPOX plus cetuximab, with pCR as the primary endpoint. While addition of cetuximab to neoadjuvant CAPOX improved overall response rate (71% v 51% after chemotherapy, $p=0.038$, and 93% v 75% after chemoradiation, $p=0.028$) and OS (HR 0.27, $p=.034$), no impact on pCR was seen (11% v. 9%, $p=0.99$).³¹ The authors concluded that while their results were promising, they could not recommend this regimen for standard use.

In conclusion, while the pCR result in our trial compared favorably to recent historical data, it neither met its pre-specified endpoint, nor produced results clinically meaningful enough to recommend addition of cetuximab to current standard neoadjuvant chemoradiation in a *KRAS*-wt, stage II-III rectal cancer population. Further genomic, proteomic and epigenetic analyses from ongoing investigations will be necessary to overcome the current lack of progress in the treatment of curable rectal cancer.

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Abbreviations

NCRT	neoadjuvant chemoradiation
pCR	pathologic complete response
wCAPOX	weekly capecitabine and oxaliplatin
EBRT	external beam radiotherapy
DFS	disease-free survival
TME	total mesorectal excision
CLIA	clinical laboratory improvement amendments

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Clinical Practice Points

- Several trials conducted in the same time period.
- Several trials conducted in the same time period have failed to show a significant increase in response rate with the addition of cetuximab to CAPOX and radiation.
- This trial confirmed findings of other similar trials.
- Further investigations of additional molecular markers may clarify the utility of cetuximab in rectal cancer.

Cycle 1: Induction Chemotherapy

Agent/Route	Day 1	Day 8	Day 15	Day 22	Day 29
Oxaliplatin IV	50 mg/m ²	50 mg/m ²		50 mg/m ²	50 mg/m ²
Cetuximab IV	250 mg/m ²	250 mg/m ²	250 mg/m ²	250 mg/m ²	250 mg/m ²
Capecitabine po	825 mg/m ² q 12 hr, M-F	825 mg/m ² q 12 hr, M-F	825 mg/m ² q 12 hr, M-F	825 mg/m ² q 12 hr, M-F	825 mg/m ² q 12 hr, M-F

Cycle 2: Chemoradiation

Agent/Route	Day 50	Day 57	Day 64	Day 71	Day 78
Oxaliplatin IV	50 mg/m ²	50 mg/m ²		50 mg/m ²	50 mg/m ²
Cetuximab IV	250 mg/m ²	250 mg/m ²	250 mg/m ²	250 mg/m ²	250 mg/m ²
Capecitabine po	825 mg/m ² q 12 hr, M-F	825 mg/m ² q 12 hr, M-F	825 mg/m ² q 12 hr, M-F	825 mg/m ² q 12 hr, M-F	825 mg/m ² q 12 hr, M-F
Pelvic Radiation*	180 cGy daily M-F	180 cGy daily M-F	180 cGy daily M-F	180 cGy daily M-F	180 cGy daily M-F

*Radiation Boost: T3 = 540 cGy in 3 fractions; T4 = 900 cGy in 5 fractions

Total Mesorectal Excision scheduled 3-8 weeks post-chemoradiation

Surgical and pathology reports submitted for central surgical review

Figure 1:
Treatment Schema

Figure 2:
Disease-Free Survival

Table 1:

Patient Demographics

Age (years)	
Median	56.4
Minimum	25.5
Maximum	77.6
Sex	
Male	53 (71%)
Female	22 (29%)
Race	
White	64 (85%)
Black	3 (4%)
Asian	6 (8%)
Native American	1 (1%)
Unknown	1 (1%)
Hispanic	
Yes	6 (8%)
No	68 (91%)
Unknown	1 (1%)

Table 2:

Selected Toxicity (N=75)

Category		Any; N (%)	Grade 3; N (%)
Gastrointestinal	Diarrhea	55 (73)	26 (35)
	Nausea	45 (60)	7 (9)
	Vomiting	17 (23)	3 (4)
	Constipation	38 (51)	4 (5)
Integument	Rash/acne	70 (93)	9 (12)
	Hand-Foot	19 (25)	2 (3)
	Mucositis (oral)	27 (36)	1 (1)
	Mucositis (anal)	6 (7)	1 (1)
Hematologic	Neutropenia	11 (15)	3 (4)
	Lymphopenia	15 (20)	8 (11)
	Anemia	26 (35)	5 (7)
Hepatic	AST/ALT/Bilirubin	45 (60)	3 (4)
Metabolic	Hypokalemia	24 (32)	8 (11)
	Hyponatremia	10 (13)	6 (8)
Neurologic	Peripheral Neuropathy	49 (65)	4 (5)
Constitutional	Anorexia	29 (39)	4 (5)
	Fatigue	56 (75)	3 (4)
	Dehydration	14 (19)	5 (7)