

Results of a Phase II Trial of Cetuximab plus Capecitabine/Irinotecan as First-Line Therapy for Patients with Advanced and/or Metastatic Colorectal Cancer

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Abstract

Background: XELIRI (capecitabine/irinotecan) is effective and well tolerated in metastatic colorectal cancer (mCRC). Cetuximab is active in mCRC alone or with chemotherapy. This study evaluated cetuximab plus XELIRI in first-line treatment of mCRC. **Patients and Methods:** Subjects had histologically confirmed unresectable colorectal adenocarcinoma (with T4 lesions) after preoperative chemoradiation and/or metastases. Treatment was capecitabine 1700 mg/m² (850 mg/m² orally twice a day on days 1-14 for 3 weeks), irinotecan 200 mg/m² intravenously (I.V.) on day 1 every 3 weeks, and weekly cetuximab (initially 400 mg/m² I.V. [120 minutes], subsequently 250 mg/m² [30 minutes]). **Results:** Baseline characteristics (N = 70): 43 men (61%); median age, 61.5 years; Eastern Cooperative Oncology Group performance status 0/1 = 66%/34%; 94% adenocarcinoma. Previous therapy: surgery (91%), chemotherapy (14%), or radiation therapy (7%). Responses (patients completing ≥ 2 cycles): complete response (5.7%), partial response (37.7%), stable disease (43.4%), and progressive disease (PD; 13.2%); 16 patients discontinued early (n = 4 allergic reaction, n = 2 withdrew consent, n = 2 death, and n = 8 other adverse events [AEs]). The overall per-protocol response rate was 43.4% (34% intent to treat [ITT]; disease control rate, 86.8%; 69% ITT). The median time to progression was 8.1 months (range, < 1-27.0 months), and the median time to response was 1.6 months (range, 1.1-8.4 months). The median survival was 20.5 months, and 45.7% of patients remain alive. Of the 38 deaths, 84% were because of PD. No death was treatment related. The most frequent grade 3/4 treatment-related AEs included diarrhea, neutropenia, and nausea/vomiting; 32% of patients required dose reductions. All patients are off the study primarily because of PD (34.3%) or AEs (40.0%). **Conclusion:** In summary, XELIRI plus cetuximab is a promising regimen that merits further study for first-line mCRC.

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Introduction

Colorectal cancer is the second leading cause of cancer death among men and women in the United States.¹ In 2008, it is estimated that

148,810 new cases will be diagnosed and an estimated 49,960 deaths from colon and rectal cancers will occur in the United States.¹

The results of the oral capecitabine (Xeloda®) and irinotecan combination (XELIRI) in the treatment of metastatic colorectal cancer (mCRC) have been previously reported.^{2,3} Cartwright et al reported a dosing strategy involving oral capecitabine plus irinotecan as a first-line treatment for mCRC.² Patients in this study (N = 49) received oral capecitabine (1000 mg/m² twice daily, 2000 mg/m² daily dose) on days 1-14 and irinotecan (240 mg/m²) on day 1 of an every-21-day cycle. In terms of clinical activity, there was 1 patient with a complete response (CR; 2%), 18 with partial responses (PRs; 43%), 20 with stable disease (SD; 48%), and 3 with progressive disease (PD; 7%), for an overall RR (ORR; CR + PR)

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of 45%. The median duration of response was 5.7 months (range, 2.8-12.3 months). The median survival was 13.4 months (range, 1.2-28.8 months), and the median progression-free survival (PFS) was 6.2 months (range, 1.2-17.5 months). Hand-foot syndrome, one of the primary dermatologic toxicities associated with the XELIRI regimen, occurred in 8 patients (16%) and was mild to moderate (grades 1 and 2). Twenty-two patients (45%) experienced National Cancer Institute (NCI) grade ≥ 3 drug-related toxicities. These investigators concluded that oral capecitabine and irinotecan given in this schedule is an active combination for the treatment of first-line mCRC. Although there was significant toxicity with the regimen, toxicity was manageable with dose reduction or dose delay.

Based on the results of previous work,² the XELIRI regimen was promising and deserved further study in subjects with advanced and/or metastatic colorectal cancer, with a reduced starting dose (capecitabine 850 mg/m² twice a day and irinotecan 200 mg/m²) for patients who might not otherwise tolerate the regimen. This high-risk group includes patients aged ≥ 70 years as well as patients with renal impairment (creatinine clearance ≥ 31 -50 mL/min). Because of reports of toxicity in an ongoing French study,⁴ both oral capecitabine and irinotecan starting doses were reduced (capecitabine 850 mg/m² twice a day and irinotecan 200 mg/m²) for all patients.

Kerr reviewed the previous European early-phase studies of oral capecitabine and irinotecan in mCRC.⁵ In a French phase I study, there were 5 dose levels, including level 1: capecitabine/irinotecan 700/200 mg/m² (n = 4), level 2: capecitabine/irinotecan 850/200 mg/m² (n = 3), level 3: capecitabine/irinotecan 1000/200 mg/m² (n = 4), level 4: capecitabine/irinotecan 1000/250 mg/m² (n = 10), and level 5: capecitabine/irinotecan 1150/250 mg/m² (n = 6). Dose-limiting toxicities were seen at level 4, and additional subjects were enrolled. Based on its clinical activity and safety profile, level 4 was selected for further study in the phase III randomized setting and was the basis for dosing in the current study until reduced dosing was recommended by DeLord et al.⁴

Cetuximab is an effective anti-epidermal growth factor receptor (EGFR) inhibitor that has shown promising clinical activity when used alone and in combination with irinotecan- or oxaliplatin-based chemotherapy. Most studies have focused on combining cetuximab with cytotoxic chemotherapy regimens that incorporated 5-fluorouracil (5-FU) as the fluoropyrimidine backbone, whereas relatively little work has been performed to combine it with capecitabine-based regimens. The goal of combining cetuximab with the XELIRI regimen was to improve the clinical activity, as determined by ORRs, and preserve the safety profile.

Patients and Methods

Patients

Patients were eligible to participate in the study if they met all of the following inclusion criteria: had histologically confirmed colorectal adenocarcinoma (proof at first diagnosis was sufficient) with T4 lesions deemed as unresectable after preoperative chemoradiation therapy and/or metastatic disease; had tissue available for assessment of EGFR expression (both EGFR-positive and EGFR-negative patients were eligible); had ≥ 1 unidimensionally measurable lesion with a diameter ≥ 20 mm using conventional computed tomography (CT) or magnetic resonance imaging scans or ≥ 10 mm using a spiral CT

scan; had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; was aged ≥ 18 years; had adequate hepatic, renal, and hematologic function as evidenced by normal laboratory values; was not pregnant or breast-feeding; and, if fertile, had agreed to use an acceptable method of birth control to avoid pregnancy for the duration of the study and for a period of 3 months thereafter.

Patients were excluded if they had received previous treatment with capecitabine, irinotecan, or cetuximab for the current cancer; had received previous chemotherapy for current disease (adjuvant chemotherapy was permitted if it had been > 6 months); had received radiation therapy other than adjuvant radiation therapy; had a creatinine clearance ≤ 30 mL/min; had a history of hypersensitivity to any of the study drugs or their components or were known to have a dihydropyrimidine dehydrogenase deficiency; had received any previous therapy that specifically and directly targeted the EGFR pathway; had a previous severe infusion reaction to a monoclonal antibody; had clinically significant cardiac disease or myocardial infarction within the past 12 months or cardiomyopathy with a decreased left ventricular ejection fraction (LVEF; $< 40\%$); had lack of integrity of the upper gastrointestinal tract, active gastrointestinal disease, or a malabsorptive disorder that could affect the metabolism of any oral medication; had impaired pulmonary function; had received concurrent immunotherapy; had undergone major surgery within past 4 weeks; had undergone major organ allografting (ie, kidney, liver, lung, heart); had evidence of central nervous system involvement; had any uncontrolled, intercurrent medical illness or uncontrolled seizures, central nervous system disorders, or clinically significant psychiatric disorder; had a history of other malignancy within the past 5 years (except cured basal cell carcinoma of the skin and carcinoma in situ of the uterine cervix); or had participated in any investigational drug study within the 4 weeks preceding the start of treatment.

Patients were not allowed to use herbal medicines, homeopathic medications, folic acid, or antioxidants, including vitamin C, vitamin E, vitamin A, and selenium, during the study and for 1 week before enrollment (ie, patients who were known to be taking one of the aforementioned alternate therapies and were not willing to discontinue use were excluded from this study). A daily multivitamin was permitted.

Study Design and Treatment Schedule

This was a phase II open-label, nonrandomized trial; all patients received the same treatment, XELIRI plus cetuximab.

The starting dose of oral capecitabine was 1700 mg/m² daily (850 mg/m² orally twice a day on days 1-14) for the general patient population. Patients who were elderly (aged ≥ 70 years) or who had renal impairment at baseline received a starting capecitabine dose of 1400 mg/m² daily (700 mg/m² orally twice a day). The dose of irinotecan administered was 200 mg/m² intravenously (I.V.) on day 1, which was given every 3 weeks, for all patients, including the elderly and renally impaired, as well as patients who had received previous pelvic radiation. Cetuximab was administered on a weekly basis. Patients received an initial loading dose of 400 mg/m² I.V. over 120 minutes, followed by weekly doses of 250 mg/m² infused over 30 minutes. Each cycle was 21 days.

As per common clinical practice, patients who had a CR could receive ≤ 2 additional cycles. Any additional treatment beyond that was

Table 1 Patient Characteristics at Baseline	
Characteristic	Number of Patients (%)
Number of Patients Enrolled	70
Sex	
Female	27 (39)
Male	43 (61)
Race	
White	55 (79)
Black	10 (14)
Hispanic	4 (6)
Native American	1 (1)
Age, Years	
Median	61.5
Range	32.2-85.4
ECOG Performance Status	
0	46 (66)
1	24 (34)
Previous Therapy	
Surgery	64 (91)
Radiation	5 (7)
Chemotherapy	10 (14)
Number of Metastatic Sites	
1	39 (56)
2	20 (29)
≥ 3	10 (14)
Metastatic Site(s)	
Liver	59 (84)
Lymph node(s)	13 (19)
Visceral/other (excludes liver)	42 (60)
Histology	
Adenocarcinoma	66 (94)
Mucinous carcinoma	3 (4)
Other	1 (1)

Abbreviation: ECOG = Eastern Cooperative Oncology Group

at the discretion of the treating physician. All other patients were to be treated until evidence of disease progression or intolerable toxicity.

The protocol was approved by a central institutional review board with jurisdiction over specific sites that registered patients in the study, and all patients were required to sign an informed consent form before being enrolled in the study.

Assessments

Confirmation of inclusion and exclusion criteria, completion of the informed consent, a pregnancy test (when indicated), and a medical history were completed at baseline. A physical examination, including vital signs, height, and weight; assessment of the ECOG PS; complete blood count with differential and platelet count; disease assessment; laboratory tests (total bilirubin, serum creatinine, aspartate aminotrans-

Table 2 Best Response After Treatment and Reasons for Nonevaluability and Study Discontinuation		
Response Evaluation Criterion	Number of Patients (%)	95% CI
Total Number Enrolled	70	—
Total Number Treated	69	—
Evaluable Patients (Per Protocol)	53	—
Best Response*		
CR	3 (6)	0-11.9
PR	20 (38)	24.7-50.7
SD	23 (43)	30.1-56.7
PD	7 (13)	4.1-22.3
NE	16	—
Disease control rate [†]	46 (87)	—
Clinical benefit rate [‡]	29 (55)	—
Reason for Nonevaluability		
Adverse event in cycle 1 or 2	12	—
Withdrew consent	2	—
Death	2	—
Reason Off Treatment		
Adverse event	28 (40)	—
PD	24 (34)	—
Investigator request	6 (9)	—
Patient request/withdrew consent	5 (7)	—
Normal completion of protocol	4 (6)	—
Death	2 (3)	—
Protocol deviation	1 (1)	—
Total Patients Surviving	32 (46)	—

*Responses (%) based on evaluable (per-protocol) patients.

[†]Disease control rate = CR + PR + SD.

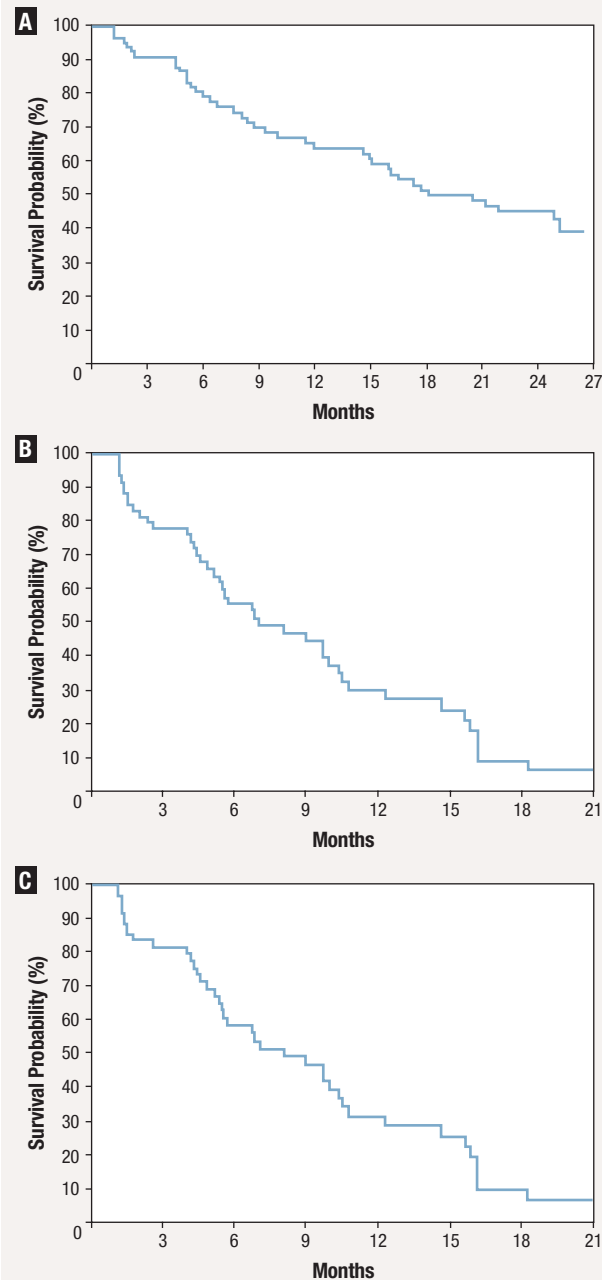
[‡]Clinical benefit rate = CR + PR + (SD ≥ 6 months).

Abbreviation: CR = complete response; NE = not evaluated; PD = progressive disease; PR = partial response; SD = stable disease

ferase, alanine transaminase, alkaline phosphatase, and serum calcium); assessment of EGFR; and assessment of quality of life (QOL) using the Functional Assessment of Cancer Therapy–Colorectal (FACT-C) standardized questionnaire were also performed at baseline. Toxicity was assessed at each patient visit and for 30 days after the last dose. Assessment of disease status (eg, CT, ultrasound, routine radiographs, bone scans) was performed every 6 weeks; confirmatory scans were required. Recommended follow-up was at 2-month intervals for 2 years (measured from the start of treatment) to collect physical and hematologic data, and to document any subsequent therapy.

Criteria for Assessing Response and Toxicity

Response Evaluation Criteria in Solid Tumors (RECIST) was used to evaluate response and progression.⁶ RECIST is based on changes in only the largest diameter (unidimensional measurement) of the tumor lesions. Best responses were determined based on the sequence of disease status with corresponding best response.

Figure 1 Overall Survival**Median Survival Time: 20.5 Months (Range, < 1-27.0 Months)**

Overall Survival		Months										Median (95% CI) Months
N	Deaths	% Survival	3	6	9	12	15	18	21	24	27	
70	38		91	81	70	64	61	52	49	46	39	20.5 (15.0-NA)

Median PFS: 7 Months (Range, < 1-27.0 Months)

Progression-Free Survival		Months										Median (95% CI) Months
N	Progression/Deaths	% PFS	3	6	9	12	15	18	21			
70	43		78	56	44	30	24	9	6			7.0 (5.3-10.3)

Median TTP: 8.1 Months (Range, < 1-27.0 Months)

Time to Progression		Months										Median (95% CI) Months
N	Progression	% TTP	3	6	9	12	15	18	21			
70	41		82	58	47	31	25	9	6			8.1 (5.5-10.5)

Abbreviations: NA = not applicable; PFS = progression-free survival; TTP = time to progression

Adverse events (AEs) were recorded throughout the trial and for ≤ 30 days after the last study treatment using the NCI Common Terminology Criteria for Adverse Events Version 3.0. The treating physician assessed the relationship of each event to treatment. Additional information about each event was collected, such as treatment required, eventual outcome, and whether therapy had to be interrupted or dosages had to be reduced.

Statistical Analysis

The primary objective of this study was to determine, based on RECIST criteria, the objective RR produced by XELIRI plus cetux-

imab in patients with mCRC.⁶ The secondary objectives of this study were to evaluate PFS and time to disease progression (for patients who progress); evaluate 1-year survival; assess the safety of this regimen in this patient population; and evaluate changes in QOL (FACT-C) and changes in the use of pain medications by these patients.

The sample size was determined using a 1-sample binomial exact method (STPlan Software). The parameters used were $p_0 = 40\%$ (null hypothesis) and $p_1 = 56\%$ (alternative hypothesis), with a significance level of 0.05 and a power of 85%, using a 1-sided test, for a total of 70 eligible patients (allowing for a 10% dropout rate).

The ORR was analyzed using descriptive methods (frequency counts

Table 3 Dosing Details

Total Number of Patients Enrolled	70		
Total Number of Patients Treated	69		
Drug	Delayed	Reduced	Discontinued
Cetuximab	35 (51%)	9 (13%)	19 (27.5%)
Irinotecan	7 (10%)	15 (22%)	1 (1%)
Oral capecitabine	41 (59%)	34 (49%)	19 (27.5%)

and proportions of response [CR + PR]). The median and range of the time to response and duration of response were also measured and were calculated for the evaluable populations; SD ≥ 16 weeks was determined. Patient baseline characteristics and disease factors were summarized using descriptive statistics. The incidence and type of treatment-related AEs were tabulated and summarized for grade 3/4 events.

Kaplan-Meier techniques⁷ in SAS were used in the intent-to-treat (ITT) population to assess times-to-event analyses such as the time to PFS and survival. Point probabilities were calculated for an every 3-month time point. For the calculation of survival, for patients who died during treatment, the last contact date was used in place of a missing death date. Similarly, the date of the last dose of treatment was used in place of a missing last contact date, if necessary.

For QOL, 4 types of subscale scores (Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being) were calculated using relevant scoring guidelines (including missing value handling, value reversion, etc), and other QOL scores, such as Trial Outcome Index, were derived based on these subscale scores. All of these QOL scores were calculated for each observation period (baseline, treatment cycle, end of treatment). For each type of QOL score, a Wilcoxon signed rank test was conducted testing the score difference between baseline and any specific observation period.

Results

Patient Characteristics

Patient demographics are summarized in Table 1. One patient was enrolled but not treated in the study because the baseline LVEF was 29% (the patient was asymptomatic). Two patients withdrew early from the study, and 14 other patients experienced toxicities before completing 2 cycles. There were 67 patients in the ITT group and 53 evaluable (per-protocol) patients.

Treatment Outcomes

The responses to study treatment for the per-protocol (evaluable) group are summarized in Table 2. Responses in the ITT group (treated/completed cycle 1) were CR in 4%, PR in 30%, and SD in 34%. The median time to response was 1.6 months (range, 1.1-8.4 months), and the median duration of response was 7.9 months (range, 1.9-14.9 months). The median survival was 20.5 months (< 1-27 months; Figure 1A), the median PFS was 7 months (range, < 1-27 months; Figure 1B), and the median time to progression (TTP) was 8.1 months (range, < 1-27 months; Figure 1C).

Drug Delivery

The median numbers of cycles completed for cetuximab, irinotecan, and oral capecitabine were 5, 5, and 6, respectively (range for all

Table 4 Adverse Events Grade ≥ 3 Occurring in > 1 Patient

Total Number of Patients Enrolled	70		
Total Number of Patients Treated	69		
Adverse Event	Grade 3	Grade 4	Total (%)
Hematologic			
Neutropenia	7	6	13 (19)
Leukopenia	2	1	3 (4)
Nonhematologic			
Diarrhea	15	1	16 (23)
Hand-foot skin reaction	5	1	6 (9)
Rash	6	0	6 (9)
Vomiting	6	0	6 (9)
Asthenia	5	0	5 (7)
Nausea	5	0	5 (7)
Dehydration	4	0	4 (6)
Anaphylaxis	1	2	3 (4)
Hypokalemia	2	1	3 (4)
Intestinal obstruction	3	0	3 (4)
Anorexia	2	0	2 (3)
Dyspnea	1	1	2 (3)
Hypomagnesemia	2	0	2 (3)
Abdominal pain	2	0	2 (3)

drugs, 1-22). A total of 51% of patients had ≥ 1 dose reduction, 68% had ≥ 1 dose delayed, 73.9% had either a delay or a reduction, and 44.9% had both a delay and a reduction. Reductions and delays were largely attributed to toxicity, specifically diarrhea. Dosing reductions and delays, by drug, are summarized in Table 3.

Toxicity

Toxicities are summarized in Table 4. Twenty-eight patients (40%) discontinued treatment because of toxicities. Patients may have experienced ≥ 1 of the following, resulting in treatment discontinuation (listed in decreasing order of frequency): diarrhea (16%), rash or hand-foot skin reaction (6%), anaphylaxis or allergic reaction (4%), dehydration (3%), intestinal obstruction (2%), cardiac event (2%), vomiting (2%), and nausea (2%). Other toxicities resulting in treatment discontinuation were only reported once (neutropenia, acute kidney failure, somnolence, stomatitis, thrombocytopenia, anorexia, abscess, spontaneous fracture, urinary tract infection, syncope, abdominal pain, and electrolyte abnormality). As of January 28, 2008, 32 patients (46%) remained alive; 38 patients had died of the following causes: PD (n = 32), cardiac arrhythmia or renal failure (n = 1 each), and other or unknown causes (no autopsy performed) (n = 2 each). No death was related to study treatment.

Quality of Life

Quality of life is summarized in Figure 2. Although few changes in overall QOL and subscales were observed throughout the study, Emotional Well-Being was statistically increased from baseline at each of cycles 1-12, indicating that patients were feeling more posi-

tive, less nervous, and more hopeful about their disease; were coping better with their illness; and were less worried about dying.

Discussion

We have previously reported on XELIRI in the treatment of mCRC.² In this earlier study, responses were seen in 45% of patients, the median duration of response was 5.7 months, PFS was 6.2 months, and the median survival was 13.4 months. A median of 6 cycles was delivered, and 80% of patients required dose reductions, mainly because of diarrhea. Dosing duration and dose reductions were nearly identical to those in the current study. Michalaki et al reported an RR of 25%, median survival of 14 months, and median PFS of 7 months.⁸ Rea et al found that the combination produced responses in 42%; the median duration of response was 7.7 months, and the median TTP was 8.3 months.⁹

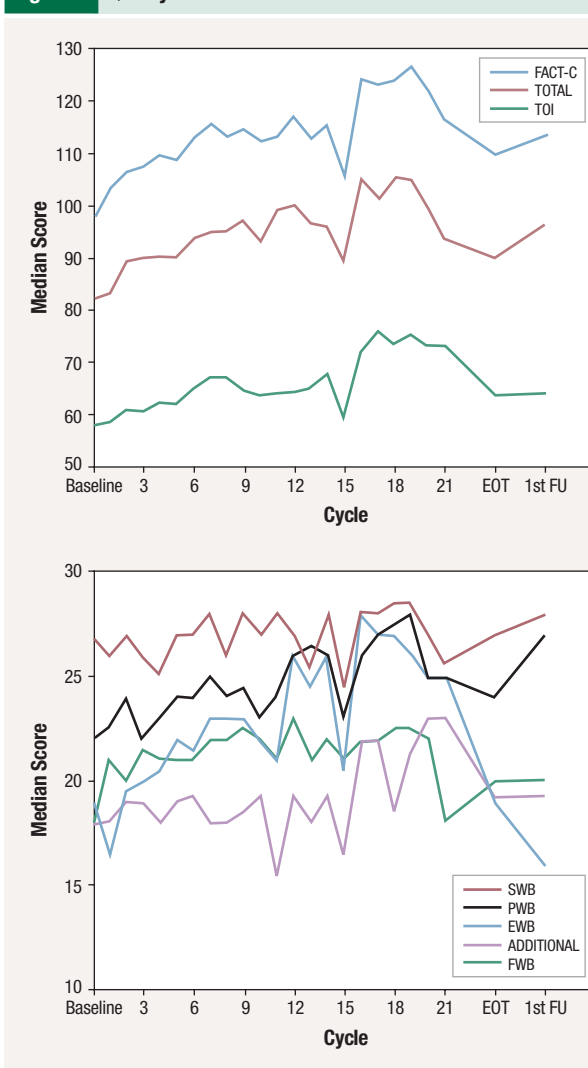
Cetuximab is effective as a single agent. It has also been shown to restore chemosensitivity to irinotecan. Single-agent cetuximab has produced RRs of 11.6%-12.4% in patients with colorectal cancer refractory to irinotecan, oxaliplatin, and a fluoropyrimidine.¹⁰ Saltz et al administered single-agent cetuximab weekly to 57 patients with chemorefractory colorectal cancer.¹¹ Responses were limited to 9% of patients; however, 21 additional patients had either minor responses or SD, for a disease control rate of 46%. The median survival was 6.4 months.

Cetuximab in combination with irinotecan has produced responses in 20% of patients and disease control in 50%, with a median PFS of 3.1 months and a median overall survival (OS) of 6 months.¹² In patients treated with cetuximab plus irinotecan as third-line therapy, responses were seen in 25% of patients, and the disease control rate was 64%. The median TTP was 4.7 months, and the median OS was 9.8 months. Cunningham et al compared cetuximab as a single-agent with cetuximab plus irinotecan.¹³ They found that the combination produced more responses (23% vs. 11%), significantly longer TTP (4.1 months vs. 1.5 months; $P < .001$), and median survival of 8.6 months versus 6.9 months. This combination has been reported by others, with similar results.¹⁴⁻¹⁸

The combination of cetuximab with irinotecan plus 5-FU has been previously reported by Folprecht et al.¹⁹ 5-Fluorouracil was given in low or high doses. Overall, 67% of patients responded, and an additional 29% had SD. The median TTP was 9.9 months, and the median survival was 33 months. This study involved weekly irinotecan ($80 \text{ mg/m}^2 \times 6$), and 5-FU dosing was limited by diarrhea. To date, there have been limited published data on the XELIRI/cetuximab regimen. Heinemann et al presented the preliminary results from a study using cetuximab with irinotecan plus capecitabine, and they showed that this combination had promising clinical activity.²⁰ This group recently updated their findings, which showed an ORR of 42%, with an overall disease control rate of 91%.²¹

At the 2007 American Society of Clinical Oncology (ASCO) Annual Meeting, Van Cutsem et al reported the results of the randomized phase III CRYSTAL (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) trial, which was a multicenter study conducted in Europe.²² A total of 1217 patients were randomized, 608 to group A (cetuximab

Figure 2 Quality of Life



Abbreviations: EOT = end of treatment; EWB = emotional well-being; FACT-C = Functional Assessment of Cancer Therapy-Colorectal; FU = follow-up; FWB = functional well-being; PWB = physical well-being; SWB = social/family well-being; TOI = Trial Outcome Index

[400 mg/m^2 initial dose, then 250 mg/m^2 per week] plus FOLFIRI every 2 weeks [irinotecan 180 mg/m^2 , leucovorin 400 mg/m^2 , 5-FU bolus 400 mg/m^2 , 5-FU infusion 2400 mg/m^2 over 46 hours]) and 609 to group B (FOLFIRI alone). The median PFS was significantly longer for patients treated with the FOLFIRI/cetuximab combination compared with patients treated with FOLFIRI chemotherapy alone (8.9 months [range, 8-9.5 months] for group A vs. 8 months [range, 7.6-9 months] for group B; $P = .036$). The addition of cetuximab reduced the relative risk of disease progression by 15%. The RR was also significantly increased by the addition of cetuximab (46.9% vs. 38.7%; $P = .005$). In general, treatment was well tolerated, with the most common grade 3/4 AEs being neutropenia (26.7% in group A, 23.3% in group B), diarrhea (15.2% and 10.5%, respectively), and skin reactions (18.7% and 0.2%, respectively). The investigators concluded that cetuximab could be safely and effectively combined with FOLFIRI chemotherapy. In fact, based on the results of this study, the combination of FOLFIRI

plus cetuximab has now been approved in Europe in the first-line setting in patients with wild-type *K-ras* disease.

In the present study, the combination of XELIRI plus cetuximab yielded promising clinical activity, with an ORR of 44%, a median duration of response of 7.9 months, a median PFS of 7.0 months, and a median survival of 20.5 months. The overall disease control rate (CR + PR + SD) was 87%; clinical benefit (CR + PR + [SD $\geq$ 6 months]) was 55%. In general, this combination was relatively well tolerated, although 80% of patients required dose reductions secondary to toxicity, which was mainly due to diarrhea. In terms of the overall safety profile, our findings are in sharp contrast to what was reported with the XELIRI regimen in the BICC-C (Bolis, Infusional, or Capecitabine with Camptosar-Celecoxib) phase III trial. In that study, reported by Fuchs et al, the XELIRI arm was associated with a significantly high incidence of grade 3/4 diarrhea (48%) and dehydration (19%).²³ A similar study conducted in Europe found that XELIRI was associated with increased mortality as well as a nearly 40% incidence of grade 3/4 diarrhea. In these 2 studies, the increased toxicity clearly impacted the clinical activity of the XELIRI regimen in a negative manner. However, it is important to note that the doses of capecitabine and irinotecan used in these studies were higher, 15% and 20%, respectively, than what was used in the present trial.

Most of the clinical studies that have investigated the combination of cetuximab with cytotoxic chemotherapy have incorporated a 5-FU backbone. As such, relatively little work has been done to study cetuximab in combination with capecitabine-based regimens. This study is important, especially in light of the recent findings of the CRYSTAL trial, which investigated the combination of FOLFIRI plus cetuximab. Although our study was a phase II study with a smaller sample size compared with the phase III CRYSTAL trial and it is always problematic to perform cross-trial comparisons, the clinical activity of XELIRI/cetuximab in terms of ORR and TTP was similar to what has been reported for FOLFIRI/cetuximab.

Conclusion

In summary, XELIRI plus cetuximab is a promising regimen that should be considered as a treatment option for the first-line treatment of mCRC and one that deserves further investigation.

Appendix

The following medical oncologists from the USON network institutions also participated in this study: Keller, Alan M., Tulsa, OK; Khandelwal, Pankaj, Odessa, TX; McCollum, Andrew D., Dallas, TX; Wehbie, Robert S., Raleigh, NC; Yoffe, Mark, Raleigh, NC; Aly, Elsayed, Indianapolis, IN; Anthony, Stephen, Spokane, WA; Archuleta, Travis D., Pueblo, CO; Armor, Jess F., Oklahoma City, OK; Arseneau, James, Hudson, NY; Brooks, Barry D., Dallas, TX; Caracandas, John, Albany, NY; Cox, John V., Dallas, TX; Cunningham, Thomas J., Troy, NY; Davis, John M., Kansas City, MO; DeMarco, Linda, Hudson, NY; Doane, Lisa L., Overland Park, KS; Ethirajan, Sukumar, Overland Park, KS; Freeman, Susan E. Myers, Aurora, CO; Greenwald, David, Kingston, PA; Jones, Vicky, Yakima, WA; Jotte, Robert, Lone Tree, CO; Kent, Elizabeth, Kansas City, KS; Kessler, John F., Newport News, VA; Knight, Clement, Columbia, MD; Kolibaba, Kathryn S., Vancouver,

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