

Cetuximab Given Every 2 Weeks plus Irinotecan Is an Active and Safe Option for Previously Treated Patients with Metastatic Colorectal Cancer

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Key Words

Cetuximab · Colorectal cancer · Irinotecan · Metastasis

Abstract

Background: We gathered data from multiple institutions on the cetuximab regimen of patients with metastatic colorectal cancer. **Methods:** 126 patients from 19 centers were included from July 2006 to July 2007 in this prospective non-controlled study. Irinotecan-refractory metastatic colorectal cancer patients with Karnofsky ≥ 70 received cetuximab 500 mg/m² every 2 weeks (q2w) in combination with irinotecan 180 mg/m² q2w until disease progression or unacceptable toxicity. The primary endpoint was the progression-free rate at 12 weeks. **Results:** Median age was 65 years; 65.9% male; colon/rectum 64.3/34.1%; Karnofsky status $\leq 80/\geq 90\%$ in 45.3/54.7% of the patients. The progression-free rate was 42.7 (95% CI 32.8–52.6) and 22.4% (95% CI 14.2–30.7) at 12 and 24 weeks, respectively. The main grade

3 or 4 toxicities were: diarrhea 13.5% and acne-like rash 10.3%. No grade 3 or 4 infusional or allergic reactions were reported. **Conclusions:** The progression-free rates confirm that cetuximab q2w in combination with irinotecan is an option, and is as active and safe as the standard weekly regimen.

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Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death in Europe, with an estimated number of deaths of >200,000 in 2006 [1]. In Spain, the CRC incidence and mortality rates are close to the median values for European countries [2].

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Approximately 50% of CRC patients will be cured following surgery and adjuvant therapy. However, the other half will develop recurrent cancer and will depend on palliative care [3, 4]. Cancer recurrence is highly associated with metastasis, and only a small proportion of these patients will be eligible for surgical resection [5]. The introduction of new antibody technologies has contributed to the increased response rate and progression-free survival of advanced CRC patients [6–8].

Cetuximab (ErbixTM) is an IgG1 chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR), active in metastatic CRC (mCRC) patients. For patients who have progressed on irinotecan-containing regimens, a randomized phase II study was performed of either cetuximab alone or in combination with irinotecan. The median time to progression for patients receiving cetuximab was 1.5 months, and the median time to progression for patients receiving irinotecan and cetuximab was 4.2 months [9]. On the basis of this study, cetuximab was approved for use in patients with mCRC refractory to irinotecan.

The currently approved dosing regimen for cetuximab is a 400-mg/m² initial dose followed by 250 mg/m² weekly (q1w). However, q1w administration would not be convenient for chemotherapy regimens administered every 2 weeks (q2w) as is common for cetuximab. In mCRC progressing on chemotherapy, irinotecan is often administered at a dose of 180 mg/m² q2w.

Preliminary findings indicate that q2w administration of cetuximab (500 mg/m²) may be a potentially convenient alternative to the approved weekly dosing regimen of 250 mg/m² (following an initial dose of 400 mg/m²) in the treatment of mCRC [10]. Cetuximab q1w and q2w have shown similar pharmacokinetic, pharmacodynamic and safety results [11, 12]. Additionally, the efficacy of the q2w regimen has also been confirmed in previous studies [13–15].

The aim of this study was to evaluate, in a multiple institution setting, the efficacy and safety of cetuximab given q2w in combination with irinotecan in previously treated irinotecan-refractory patients with mCRC.

Patients and Methods

Study Design and Entry Criteria

This open-label, non-randomized, prospective, multicenter study was conducted in 19 Spanish centers from July 2006 to July 2007. The study population consisted of patients with histologically confirmed CRC and non-resectable metastatic disease which was irinotecan refractory, and a Karnofsky performance status

index of ≥ 70 . EGFR testing was not mandatory and K-ras status was not studied because its predictive value regarding cetuximab response at the beginning of the trial was not known. Eligibility criteria also included: age ≥ 18 years; presence of at least one lesion with at least one measurable dimension (index lesions were not in a previously irradiated zone); ability to tolerate irinotecan treatment; recovery from major toxicity following previous chemotherapy; effective contraception if fertile; AST and ALT levels $\leq 2.5 \times$ ($\leq 5 \times$ if hepatic metastasis) the upper limit of normal (ULN); total serum bilirubin level $< 1.5 \times$ the ULN; creatinine levels $\leq 1.5 \times$ the ULN; neutrophil count $\geq 1.5 \times 10^9/l$; platelet count $\geq 100 \times 10^9/l$, and hemoglobin ≥ 9 g/dl. Patients who had received more than two previous lines of chemotherapy for advanced disease were excluded.

Patients were recruited in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to undertaking any study procedure.

Therapy

Cetuximab was administered as a 150-min intravenous infusion at 500 mg/m² q2w. The maximum infusion rate allowed was 10 mg/min (5 ml/min). Five minutes prior to the infusion of cetuximab we prescribed 5 mg intravenous dexchlorfeniramine. Irinotecan was administered 1 h after the cetuximab infusion as a 30/90-min intravenous infusion at 180 mg/m² q2w. Irinotecan dose changes were according to official prescribing information. Therapy was maintained until disease progression or unacceptable toxicity.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Treatment modifications were indicated for severe skin toxicity and hypersensitivity reactions. In the event of grade 4 skin toxicity, the patient was withdrawn from the study. In case of grade 3 skin toxicity, cetuximab was discontinued until the toxicity resolved to grade 2 or less, at which time it was resumed. If the toxicity did not resolve to at least a grade 2 within 6 weeks (delaying 3 consecutive infusions) cetuximab was discontinued. After resumption, cetuximab was administered at 250 mg/m² q1w until the next irinotecan infusion. If the grade 3 toxicity recurred at least four times, cetuximab was discontinued. A second or third recurrence of a grade 3 toxicity required permanent dose reductions of 100 mg/m² each time. For hypersensitivity reactions of grade 1 severity, the infusion rate was reduced by 50%. For grade 2 hypersensitivity reactions, cetuximab was discontinued and symptomatic measures were undertaken until the toxicity resolved to grade 1 or less, at which time cetuximab was resumed at 50% of the initial dose. Cetuximab was discontinued for grade 3 or 4 hypersensitivity reactions.

Evaluation of Patients

The evaluation of disease progression was performed locally according to the Response Evaluation Criteria in Solid Tumors (RECIST) system [16] using computerized tomography or magnetic resonance imaging technique at screening and every 12 weeks using the same method. In all cases this clinical study was developed in agreement with the clinical practice of the study centers. Safety was assessed continuously throughout the study by monitoring adverse events.

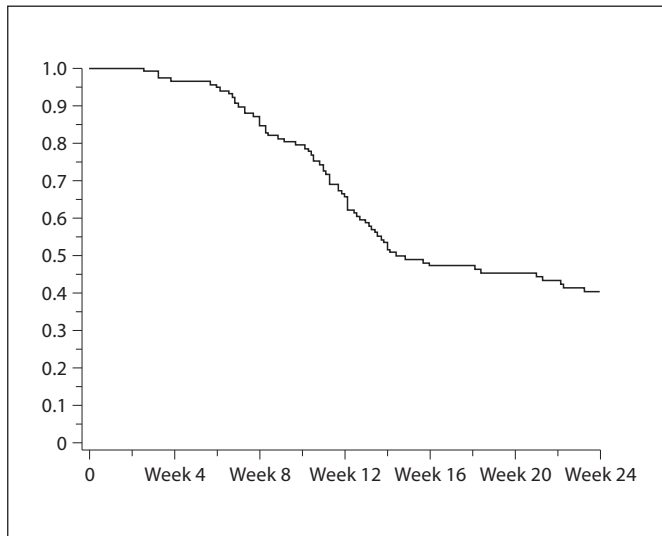


Fig. 1. Kaplan-Meier curve for the PF survival of the ITT population. PF survival at 12 weeks was 65.7% (95% CI 56.3–73.5), and at 24 weeks 40.5% (95% CI 31.4–49.4).

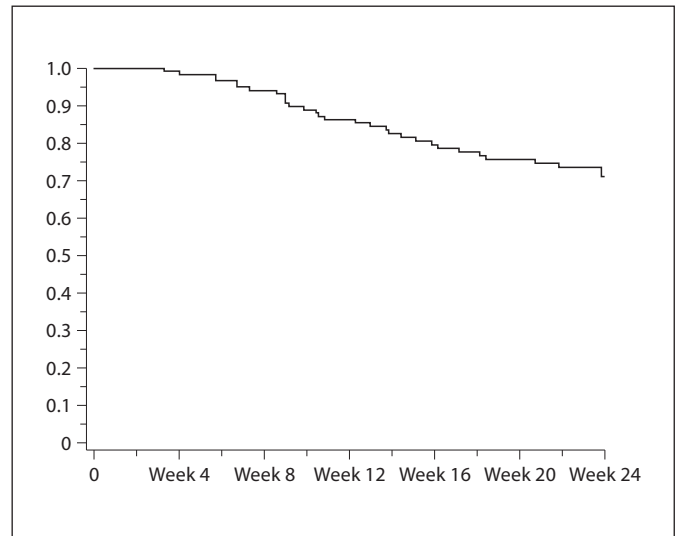


Fig. 2. Kaplan-Meier curve for the overall survival of the ITT population. Overall survival rate at 12 weeks was 86.3% (95% CI 78.6–92.4), and at 24 weeks 71.1% (95% CI 61.3–78.8).

Statistical Analysis

The primary endpoint of this trial was the proportion of patients who were progression-free (PF) at 12 weeks. The PF rate at 12 weeks was expected to be 50%. With a minimum enrollment of 120 patients, the 95% CI was estimated to be a maximum of 9%.

Secondary endpoints, other than toxicity, were the PF rate at 24 weeks, PF survival and overall survival. The PF rates were estimated by dividing the number of patients who had not progressed within 12 (or 24) weeks by the total number of evaluable patients. Loss to follow-up was considered as progression at the date of last contact unless documentation proved otherwise. Time to progression was calculated from the day of inclusion to disease progression or death. Time to death (i.e., survival) was calculated from the day of inclusion to death. Time to progression, time to death, PF and overall survival were estimated using the Kaplan-Meier method [17].

All patients who received at least one dose of cetuximab in combination with irinotecan were considered evaluable for efficacy and safety (intention-to-treat, ITT, population).

Statistical analyses were performed using the Statistical Analysis System (SAS) software, version 9.1.3.

Results

Patient Characteristics

A total of 126 previously treated irinotecan-refractory patients with mCRC were included in the ITT population. Baseline demographic data for the ITT population are shown in table 1.

Table 1. Patient characteristics (n = 126)

Characteristic	Number of patients
Sex	
Male	83 (65.9%)
Female	43 (34.1%)
Median age, years (range)	65 (35–85)
Karnofsky performance status	
≤80	57 (45.2%)
≥90	69 (54.8%)
Median time since CRC diagnosis, months (range)	20.1 (3.7–117.8)
Median time since mCRC diagnosis, months (range)	17.4 (0.0–82.1)
Primary site	
Colon	81 (64.3%)
Rectum	43 (34.1%)
Colon and rectum	2 (1.6%)
Metastatic site(s)	
Liver	88 (69.8%)
Lung	74 (58.7%)
Liver and lung	55 (43.7%)
Lymph nodes	35 (27.8%)
Suprarenal glands	11 (8.7%)
Median number of metastatic site(s) (range)	2 (1–5)
Prior chemotherapy (1 line)	12 (9.5%)
Prior chemotherapy (2 lines)	114 (90.5%)
Prior adjuvant therapy	57 (45.2%)
Prior radiation therapy	16 (12.7%)

Efficacy

The PF rate after 12 weeks was 42.7% (95% CI 32.8–52.6), and at 24 weeks it was 22.4% (95% CI 14.2–30.7).

The median time to disease progression from the day of inclusion, estimated in this study, was 14.4 weeks; with a 12-week PF survival of 65.7% (95% CI 56.3–73.5) and a PF survival of 40.5% (95% CI 31.4–49.4) after 24 weeks (fig. 1).

Thirty-one patients (24.6%) died during the 24-week follow-up period. The overall survival was 86.3% (95% CI 78.6–91.4) and 71.1% (95% CI 61.3–78.8) at 12 and 24 weeks, respectively (fig. 2).

Safety

A total of 114 patients (90.5%) experienced at least one adverse event related to cetuximab and/or irinotecan (40.5% grade 3 or 4).

Toxicities related to cetuximab and/or irinotecan that occurred with a frequency of >10% are shown in table 2. Acne-like rash, often described as folliculitis, septic rash, acne or dermatitis, was the most frequent adverse event (57.9%; 10.3% grade 3 or 4). Diarrhea and asthenia were the most frequent adverse events related to treatment, and the main grade 3 or 4 toxicities were: diarrhea 13.5% and acne-like rash 10.3%. No grade 3 or 4 infusional or allergic reactions were reported during the follow-up period of 24 weeks.

Cetuximab q2w was not associated with a greater incidence of grade 3–4 adverse events than cetuximab q1w, according to the previously published experience.

Discussion

Treatment alternatives for patients with CRC after failure of oxaliplatin and irinotecan in combination with fluorouracil or fluoropyrimidines, are indeed limited. The approved indication for the use of cetuximab was restricted to those patients with mCRC who expressed EGFR and had failed an irinotecan-based chemotherapy regimen at the time of developing this trial. Assessing EGFR expression to predict response to treatment with cetuximab in mCRC patients is currently being questioned since several authors have described responses in EGFR-negative patients [18–20]. In our study, EGFR testing was not mandatory and inclusion of EGFR-negative patients was allowed.

Recently, K-ras status has been confirmed as a predictive factor of cetuximab response. This information was not provided during the development of this trial. None-

Table 2. Most frequent (>10%) adverse events related to cetuximab and/or irinotecan (n = 126)

Adverse event	Total, n (%)	Grade 3 or 4, n (%)
Acne-like rash	73 (57.9)	13 (10.3)
Diarrhea	60 (47.6)	17 (13.5)
Asthenia	38 (30.2)	9 (7.1)
Neutropenia	15 (11.9)	4 (3.2)
Vomiting	18 (14.3)	3 (2.4)
Anemia	29 (23.0)	1 (0.8)
Alopecia	18 (14.3)	1 (0.8)
Mucositis	14 (11.1)	2 (1.6)

theless, our final results (efficacy and safety of cetuximab q2w) are similar to other studies with cetuximab given q2w where K-ras status was not performed [11, 12].

In addition, the currently approved dosing regimen for cetuximab is an initial infusion of 400 mg/m² followed by weekly doses of 250 mg/m². In spite of this, many commonly used chemotherapy agents for mCRC, with which cetuximab is commonly combined, including irinotecan, are administered on a q2w basis. The option to synchronize the administration of cetuximab and concomitant chemotherapy would reduce the patient's visits to hospital and simplify treatment administration, thus being desirable for both patients and healthcare professionals.

In this study, cetuximab administered q2w in combination with irinotecan is an option that is as active and safe as the standard q1w regimen, confirming the results of previous studies [10–12].

Nonetheless, it would be desirable to confirm the efficacy equivalence of the two dosing schedules in a non-inferiority randomized trial of a q1w versus q2w regimen of cetuximab.

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References

- 1 Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P: Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;18:581–592.
- 2 Parkin DM, Bray F, Ferlay J, Pisani P: Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001;94:153–156.
- 3 Matsumoto S, Nishimura T, Kanai M, Mori Y, Nagayama S, Kawamura J, Nomura A, Miyamoto S, Kitano T, Ishiguro H, Yanagihara K, Teramukai S, Sakai Y, Chiba T, Fukushima M: Safety and efficacy of modified FOLFOX6 for treatment of metastatic or locally advanced colorectal cancer. A single-institution outcome study. *Chemotherapy* 2008;54:395–403.
- 4 Sadahiro S, Suzuki T, Maeda Y, Ishikawa K, Yasuda S, Makuuchi H, Murayama C: Phase I/II study of 24-hour infusion of irinotecan combined with oral UFT for metastatic colorectal cancer. *Chemotherapy* 2008;54:140–146.
- 5 National Cancer Institute, US National Institutes of Health: Colon cancer treatment (PDQ®). <http://www.cancer.gov/cancertopics/pdq/treatment/colon/healthprofessional>.
- 6 Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pinter T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P: Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408–1417.
- 7 Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ, Zalcberg JR: K-ras Mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008;359:1757–1765.
- 8 Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P: Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009;27:663–671.
- 9 Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337–345.
- 10 Tabernero J, Pfeiffer P, Cervantes A: Administration of cetuximab every 2 weeks in the treatment of metastatic colorectal cancer: an effective, more convenient alternative to weekly administration? *Oncologist* 2008;13:113–119.
- 11 Tabernero J, Cervantes A, Martinelli E, Vega-Villegas E, Rojo F, Pérez-Fidalgo A, Casado E, Ciardiello F, Zubel A, Baselga J: Optimal dose of cetuximab (C) given every 2 weeks (q2w): a phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of weekly (q1w) and q2w schedules in patients (pts) with metastatic colorectal cancer (mCRC) (abstract 3085). *J Clin Oncol* 2006;24(suppl):18s.
- 12 Ciardiello F, Cervantes A, Vega-Villegas M, Casado E, Rodriguez-Braun E, Martinelli E, Rojo F, Baselga J, Kisker O, Tabernero J: Optimal dose for an every 2 week (q2w) cetuximab (C) regimen in patients (pts) with metastatic colorectal cancer (mCRC): a phase I safety, pharmacokinetics (PK) and pharmacodynamics (PD) study of weekly (q1w) and q2w schedules. *Eur J Cancer* 2007(suppl 5):247.
- 13 Pfeiffer P, Bjerregaard JK, Qvortrup C, Jensen BV, Yilmaz M, Nielsen D: Simplification of cetuximab (Cet) administration: double dose every second week as a 60 minute infusion (abstract 4133). *J Clin Oncol* 2007;25(suppl):18s.
- 14 Pfeiffer P, Nielsen D, Bjerregaard J, Qvortrup C, Yilmaz M, Jensen B: Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. *Ann Oncol* 2008;19:1141–1145.
- 15 Martín-Martorell P, Roselló S, Rodríguez-Braun E, Chirivella I, Bosch A, Cervantes A: Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. *Br J Cancer* 2008;99:455–458.
- 16 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205–216.
- 17 Kaplan EL, Meier P: Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1959;53:457–481.
- 18 Vallböhmer D, Zhang W, Gordon M, Yang DY, Yun J, Press OA, Rhodes KE, Sherrod AE, Iqbal S, Danenberg KD, Groshen S, Lenz HJ: Molecular determinants of cetuximab efficacy. *J Clin Oncol* 2005;23:3536–3544.
- 19 Scartozzi M, Bearzi I, Berardi R, Mandolesi A, Fabris G, Cascinu S: Epidermal growth factor receptor (EGFR) status in primary colorectal tumors does not correlate with EGFR expression in related metastatic sites: implications for treatment with EGFR-targeted monoclonal antibodies. *J Clin Oncol* 2004;22:4772–4778.
- 20 Chung KY, Shia J, Kemeny NE, Shah M, Schwartz GK, Tse A, Hamilton A, Pan D, Schrag D, Schwartz L, Klimstra DS, Fridman D, Kelsen DP, Saltz LB: Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J Clin Oncol* 2005;23:1803–1810.