Original Study

FOLFOX4 With Cetuximab vs. UFOX With Cetuximab as First-Line Therapy in Metastatic Colorectal Cancer: The Randomized Phase II FUTURE Study

Jean-Yves Douillard,[1] Tomasz Zemelka,[2] George Fountzilas,[3] Carlo Barone,[4] Michael Schlichting,[5] Jim Heighway,[6] S. Peter Eggleton,[5] Vichien Srimuninnimit[7]

Abstract

In this randomized phase II study, we compared 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX4) with cetuximab with UFOX (UFT, leucovorin, and oxaliplatin) with cetuximab as first-line treatment for metastatic colorectal cancer (mCRC). We found that UFOX with cetuximab had an acceptable safety profile but inferior activity compared with FOLFOX4 with cetuximab. UFT should not be used in combination with oxaliplatin and cetuximab in this setting.

Introduction: The purpose of this study was to assess the efficacy and safety of FOLFOX4, comprising infusional 5-fluorouracil (5-FU)/leucovorin (LV) and oxaliplatin, with cetuximab compared with UFOX, comprising UFT, an oral prodrug of 5-FU, LV, and oxaliplatin, with cetuximab as first-line treatment for mCRC. **Patients and Methods:** Patients, unselected by tumor *KRAS* status, were randomized 1:1 to FOLFOX4 with cetuximab or UFOX with cetuximab. Treatment was continued until disease progression or unacceptable toxicity. The primary end point, assessed in the intention-to-treat population, was progression-free survival (PFS). Secondary end points included tumor response, overall survival, and safety. Outcome according to *KRAS* mutation status was investigated. **Results:** Recruitment was curtailed at 302 patients after reporting of the importance of tumor *KRAS* mutation status for cetuximab activity. Baseline characteristics were balanced between treatment groups. PFS was significantly longer in the FOLFOX4 with cetuximab group compared with UFOX with cetuximab group (median 8.2 vs. 6.6 months; hazard ratio, 0.68; 95% confidence interval [CI], 0.52-0.89; $P = .0048$). The response rate was also significantly greater in the FOLFOX4 with cetuximab group (51.3% vs. 37.5%, respectively; odds ratio, 1.76; 95% CI, 1.11-2.78; $P = .0160$), although overall survival was comparable. In the *KRAS* wild type subgroup, efficacy outcomes were similar to those in the intention-to-treat population. Side effect profiles were manageable and consistent with expectations. **Conclusion:** In the first-line treatment of mCRC, UFOX with cetuximab had an acceptable safety profile but inferior activity compared with FOLFOX4 with cetuximab in relation to PFS and response. The regimens were comparable with regard to overall survival.

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Introduction

Infusional 5-fluorouracil (5-FUCI), administered with the biomodulator leucovorin (LV), remains a key component of chemotherapy combinations used in the first-line treatment of metastatic colorectal cancer (mCRC). Such regimens include 5-FUCI/LV with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI),

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[1]Institut de Cancerologie de l'Ouest - Centre René Gauducheau, Saint-Herblain, France
[2]Centrum Onkologii, Instytut im. M. Sklodowskiej-Curie, Krakow, Poland
[3]Department of Medical Oncology, Aristotle University of Thessaloniki School of Medicine, Papageorgiou Hospital, Thessaloniki, Greece
[4]UOC di Oncologia Medica, Università Cattolica del S. Cuore, Rome, Italy
[5]Merck KGaA, Darmstadt, Germany
[6]Cancer Communications and Consultancy Ltd, Knutsford, Cheshire, UK
[7]Siriraj Hospital, Bangkok, Thailand

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Address for correspondence: Jean-Yves Douillard, MD, PhD, Department of Medical Oncology, ICO R. Gauducheau, Bd J. Monod, 44805 St Herblain, France
Fax: +33-240-679-776; e-mail contact: jean-yves.douillard@ico.unicancer.fr

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combinations that are considered broadly comparable in relation to efficacy.[1-4] Randomized studies have shown that the addition of epidermal growth factor receptor (EGFR) monoclonal antibodies to 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX4) or FOLFIRI improves efficacy in the treatment of patients whose tumors are wild type at exon 2 codons 12 and 13 of the *KRAS* gene.[5-7]

In an attempt to maximize patient benefit by minimizing toxicity and the inconvenience of 5-FUCI,[8] orally deliverable prodrugs of 5-fluorouracil (5-FU) have been developed. One such compound is UFT, which comprises the prodrug tegafur, combined in a 1:4 molar ratio with a second molecule, uracil, which acts as a competitive inhibitor of the primary catabolic enzyme of 5-FU, dihydropyrimidine dehydrogenase.[9-11] Experimental models suggested that the anticancer activity of UFT combined with LV was more effective than that of UFT alone.[12-14] In a phase III randomized study, oral UFT with oral LV was compared with bolus 5-FU/LV and was shown to provide an equally effective but safer and more convenient first-line treatment alternative for patients with mCRC.[15] In the same setting, a second phase III study failed to demonstrate an efficacy benefit for UFT/LV compared with bolus 5-FU/LV but did confirm substantial safety benefits for patients in the UFT/LV group.[16]

A series of phase II studies subsequently evaluated the efficacy and safety profile of UFT/LV combined with oxaliplatin in the first- or subsequent-line treatment of mCRC.[17-21] These studies showed that oxaliplatin could be combined safely with UFT/LV (UFOX) and that such regimens were active and convenient to administer. The favorable safety profile of UFOX suggested the possibility of combining this chemotherapy regimen with a targeted biological agent, such as the EGFR antibody, cetuximab.

A phase II study of cetuximab combined with FOLFOX4 initially suggested that this regimen was a highly active first-line treatment for mCRC.[22] The current study, FOLFOX4 Plus Cetuximab vs. UFOX Plus Cetuximab (FUTURE), was therefore designed as an exploratory study to compare the efficacy and safety of FOLFOX4 and UFOX both with cetuximab in the first-line treatment of patients with mCRC. The study was designed and implemented before the demonstration of the predictive significance of tumor *KRAS* mutation status in patients with mCRC receiving cetuximab; therefore, enrollment was independent of this biomarker.

Patients and Methods

Patient Eligibility

Patients with a histologically confirmed adenocarcinoma of the colon or rectum were eligible for inclusion if they were $\geq$ 18 years of age, with a first occurrence of metastatic disease not curatively resectable at presentation, a Karnofsky performance status (KPS) of $\geq$ 60% at study entry and a life expectancy of $\geq$ 3 months. Baseline presence of at least 1 lesion unidimensionally measurable using computed tomography (CT) and/or magnetic resonance imaging (MRI) was also required, as was adequate organ function as denoted by: a white blood cell count $\geq 3 \times 10^9$/L, with neutrophils $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin $\geq$ 9 g/dL; aspartate aminotransferase and alanine aminotransferase $\leq$ 2.5 $\times$ upper limit of normal (ULN; $\leq$ 5 $\times$ ULN if liver metastasis was present) range; normal serum creatinine levels (in the case of elevated creatinine, labeled ethylenediaminetetraacetic acid (EDTA) clearance $\geq$ 65 mL/min was acceptable). The availability of a tumor biopsy or archived tumor sample was also an eligibility requirement as was, if relevant, the use of effective contraception methods.

Patients were excluded if they had known or suspected brain metastases and/or leptomeningeal disease, or if they had previously received chemotherapy for colorectal cancer (except adjuvant therapy with progression of disease documented $>$ 6 months after the end of treatment), or previous oxaliplatin-based chemotherapy. They were also excluded if they had received surgery (excluding diagnostic biopsy) or irradiation within 4 weeks before randomization; concurrent or previous chronic systemic immune therapy, targeted therapy, anti-vascular endothelial growth factor therapy, or EGFR-pathway-targeting therapy or concurrent hormonal therapy not indicated in the clinical trial protocol (except for physiologic replacement or contraception). Patients were to have neither known hypersensitivity reaction to any of the components of study treatment nor any concurrent malignancy, other than basal cell cancer of the skin, or preinvasive cancer of the cervix (patients with a previous malignancy but without evidence of disease for $\geq$ 5 years were eligible). Other exclusion criteria included pregnancy, known drug abuse/alcohol abuse, legal incapacity or limited legal capacity, the existence of a medical or psychological condition which in the opinion of the investigator would not have permitted the patient to complete the study or sign meaningful informed consent or the presence of significant disease which, in the investigator's opinion, would have excluded the patient from the study. Participation in another clinical study within the 30 days before randomization also led to exclusion.

The study was reviewed and approved by an independent ethics committee at each investigational site and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before any study-related activities were carried out.

Study Design

This was a multicenter, randomized, open-label, phase II study to assess the efficacy and safety of FOLFOX4 with cetuximab compared with UFOX with cetuximab in the first-line treatment of mCRC. After baseline evaluations, eligible patients were randomly assigned to 1 of the 2 treatment groups in a 1:1 ratio, stratified according to Köhne's criteria,[23] using a centralized stratified permuted block randomization procedure. KPS documented at baseline was converted into the corresponding Eastern Cooperative Oncology Group performance status to allow this risk stratification. The FUTURE study is registered with Clinical Trials.gov, number NCT00439517.

On day 1 of a 28-day cycle, patients received cetuximab (initial dose of 400 mg/m^2 infused over 2 hours, and 250 mg/m^2, weekly over 1 hour, thereafter) followed by either FOLFOX4: intravenously: oxaliplatin 85 mg/m^2, days 1, and 15; LV 200 mg/m^2 followed by 5-FU 400 mg/m^2 bolus, followed by 600 mg/m^2 infused over 22 hours, on days 1, 2, 15, and 16; or UFOX: intravenously: oxaliplatin 85 mg/m^2, days 1, and 15; orally: UFT (tegafur 250 mg/m^2/d, uracil 560 mg/m^2/d; in 3 divided doses, rounded to the nearest number of whole capsules) and oral LV 90 mg/d, in 3 divided doses; on days 1-21. This particular regimen of UFT and oxaliplatin was chosen to allow a 4-week dosing cycle, which ensured that all assessments were carried out at the same time in each treatment arm. The schedule also ensured that any synergy

between oxaliplatin and tegafur was maximized through the dosing of tegafur on all days when oxaliplatin was given.

Treatment was continued until either progression of disease, withdrawal of consent, the occurrence of unacceptable toxicity even after dosage reduction, or the investigator decided that it was no longer in the patient's best interest to continue treatment. Crossover before progression in case of intolerance to UFT or 5-FU was not permitted. Investigators assessed response to treatment every 8 weeks based on radiological imaging (CT or MRI scans) according to Response Evaluation Criteria in Solid Tumors 1.0 guidelines.[24] After permanent treatment cessation, patients were followed every 3 months to collect data on progression, survival, and subsequent lines of treatment.

The primary end point was progression-free survival (PFS). Secondary end points included response, overall survival, safety, and quality of life. The clinical cutoff for the primary analysis (June 30, 2009) was prespecified as 12 months after the enrollment of the last patient. The analysis of overall survival was based on data from a longer follow-up time, with a cutoff date of August 31, 2011.

In an additional analysis, the tumor mutation status of *KRAS* exon 2 codons 12 and 13 was assessed using the TheraScreen K-RAS Mutation Kit (DxS). Assessment of treatment outcome according to *KRAS* mutation status was subsequently carried out in patients for whom an evaluable tissue sample was available (*KRAS* population).

Statistical Methods and Considerations

The primary objective of this study was to compare PFS in patients receiving cetuximab with either UFOX or FOLFOX4 as initial treatment for mCRC. All analyses were regarded as exploratory. The primary efficacy analysis of PFS, defined as the duration from randomization until first observation by the investigator of radiologically confirmed progression, or death from any cause occurring within 12 weeks of the last tumor response assessment or randomization (whichever was later), was carried out on the intention-to-treat (ITT) population, comprising all randomized patients. In general, comparisons of treatment groups in relation to time-to-event data were carried out using 2-sided stratified log-rank tests taking strata used for randomization into account (low-, medium-, and high-risk according to Köhne's criteria). Stratified hazard ratios (HRs) were calculated by applying a Cox proportional hazard model. The product limit method (Kaplan-Meier estimates) was used for estimation of the medians in relation to time-to-event variables. Best overall response rate and disease control rate were analyzed using Cochran-Mantel-Haenszel tests taking the strata used for randomization into account. Hazard and odds ratios were calculated for FOLFOX4 with cetuximab over UFOX with cetuximab.

Safety analyses were performed on the safety population, which comprised all randomized patients who received any dose of any study treatment. Adverse events were coded according to the Medical Dictionary for Regulatory Activities version 12.0 and summarized according to worst Grade per patient according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

Given the exploratory objectives of this study, sample size considerations were not based on power considerations and no a priori hypothesis was formulated. The initial plan was to enroll 420 patients overall, which assuming a 5% dropout rate, would have led to approximately 200 patients in each treatment arm.

Role of the Study Sponsor

The clinical study was designed by Merck KGaA, the study sponsor, in collaboration with J.-Y.D. The sponsor was responsible for data management and statistical analysis. The drafting of this report was commissioned by the sponsor. All authors had full access to all relevant study data and J.-Y.D. had final responsibility for the decision to submit for publication.

Results

Patient Characteristics

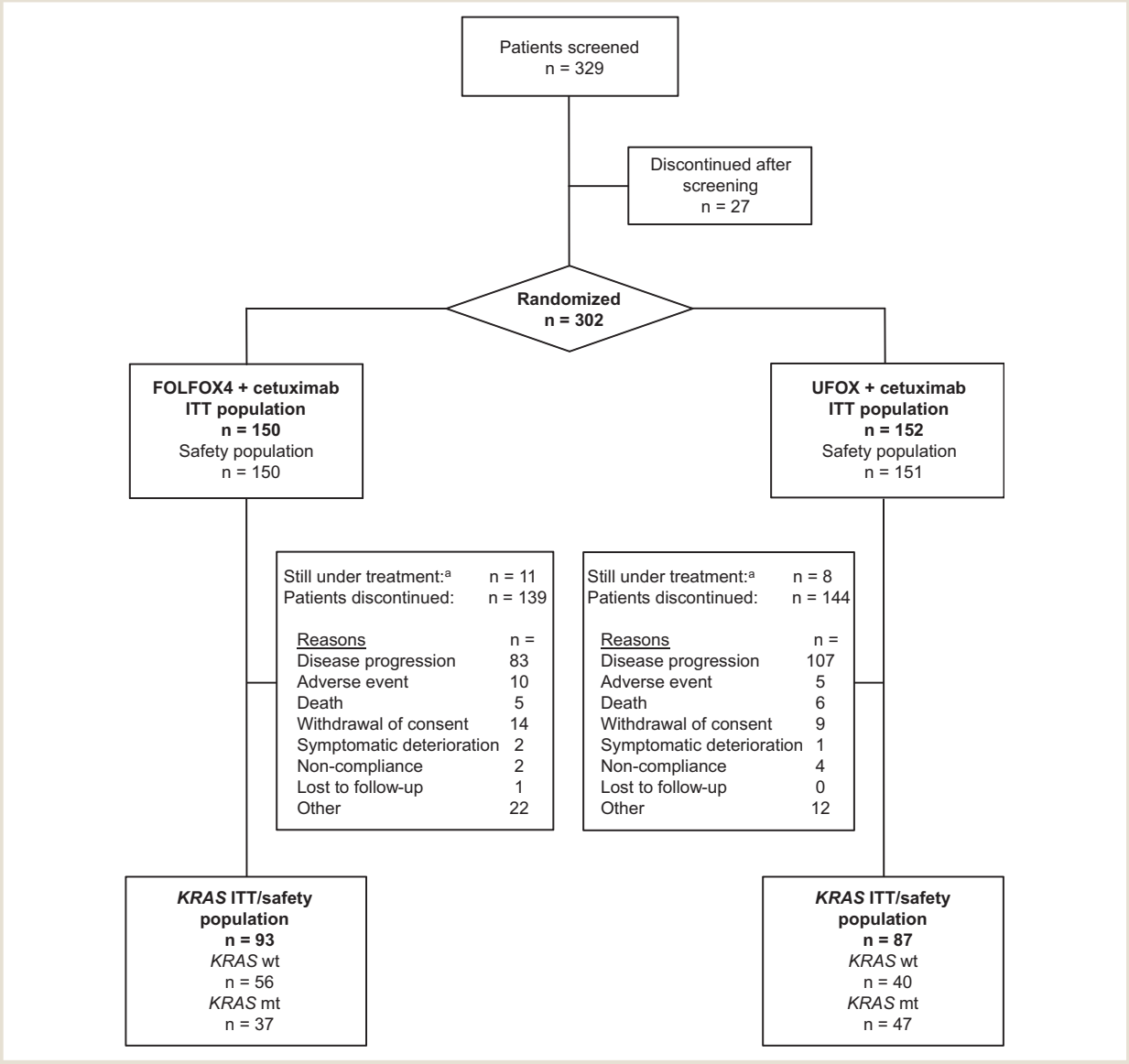
Figure 1 shows the study profile. In total, 329 patients were screened for study eligibility at 51 centers in 13 countries. The first patient was randomized and enrolled on February 12, 2007 and the last on June 30, 2008. Enrollment was subsequently halted after the reporting of the data from 2 randomized studies which confirmed the importance of tumor *KRAS* mutation status in relation to cetuximab activity in the first-line treatment of mCRC.[25,26] Of the 329 screened patients, 30 were deemed ineligible for study entry by the investigators. However, 3 of these 30 patients still entered the study, giving a total of 302 patients in the ITT population; with 150 randomly assigned to the FOLFOX4 with cetuximab group and 152 to the UFOX with cetuximab group. Baseline characteristics were generally balanced between treatment groups. One patient in the UFOX with cetuximab group withdrew consent before receiving any dose of study treatment and was subsequently excluded from the safety population (n = 301).

Tumor samples evaluable for *KRAS* mutation status were available from 180 of 302 patients (60%; hereafter referred to as the *KRAS* population) of the ITT population. Baseline characteristics for the *KRAS* population were balanced between treatment arms and were comparable with those of the ITT population. In this context, the *KRAS* population appeared therefore to be a representative sample of the ITT population. Codon 12 or 13 mutations were identified in the tumors of 84 of 180 patients (47%) and 96 of 180 tumors (53%) were scored as *KRAS* wild type. Mutations were more commonly identified in the UFOX with cetuximab (47 of 87; 54%) compared with the FOLFOX4 with cetuximab group (37 of 93; 40%). Although baseline characteristics were generally balanced between the treatment arms of the *KRAS* wild type and *KRAS* mutant populations, some minor imbalances, which were unlikely to have had any effect, were apparent (Table 1).

Treatment Compliance

Treatment compliance is summarized in Table 2. In the FOLFOX4 with cetuximab group, the median duration of treatment with 5-FU was 25.1 weeks and 59% of patients had a relative dose intensity of $\geq$ 80%. In the UFOX with cetuximab group, the median duration of treatment with UFT was 23.7 weeks. Because of a flaw in the design of the case report forms, reliable dosing data for tegafur were available for only 115 of 151 (76%) patients. The demographic characteristics of this group were examined informally and appeared not to differ substantially from those of the overall population (data not shown); 74% of evaluable patients had a relative dose intensity for tegafur of $\geq$ 80%. Exposure to oxaliplatin and cetuximab measured using relative dose intensity was greater in the UFOX with cetuximab compared with the FOLFOX4 with cetuximab group (Table 2). In the *KRAS* wild type subpopulation, comparable

Figure 1 Disposition of Patients and Acquisition and Analysis of Clinical Samples



Abbreviations: FOLFOX4 = 5-fluorouracil, leucovorin and oxaliplatin; ITT = intention-to-treat; mt = mutant; UFOX = UFT, leucovorin, and oxaliplatin; UFT = tegafur and uracil; wt = wild type.
[a]At clinical cutoff of June 30, 2009.

levels of exposure to fluoropyrimidine were seen. Relative dose intensities ≥ 80% for evaluable patients in the FOLFOX4 with cetuximab group (n = 56) and UFOX with cetuximab group (n = 31) were reported for 63% and 87% of patients receiving 5-FU and tegafur, respectively.

Efficacy

Efficacy data are summarized in Table 3. In the primary analysis, PFS in the ITT population was significantly longer in the FOLFOX4 with cetuximab group compared with the UFOX with cetuximab group (median 8.2 vs. 6.6 months, respectively; stratified HR, 0.68, 95% confidence interval (CI), 0.52-0.89; $P = .0048$; Fig. 2A). Best overall response was also significantly enhanced in the FOLFOX4 with cetuximab group compared with the UFOX with cetuximab group (51.3% vs. 37.5%, stratified odds ratio, 1.76; 95% CI, 1.11-2.78; $P = .0160$) and the median duration of response was longer (8.7 vs. 5.6 months), although disease control rates were similar (85.3% vs. 82.2%). Overall survival was also similar between the treatment groups (median 18.4 vs. 16.8 months, respectively; stratified HR, 0.98; 95% CI, 0.76-1.26; $P = .86$; Fig. 2D). Five patients in each treatment group of the ITT population (3%) underwent R0 resection of metastatic lesions. Anticancer therapy during the follow-up period appeared to be balanced between the treatment groups (Supplemental Table 1).

In the *KRAS* population and subpopulations, the differences in treatment effect between treatment groups were broadly similar to those

Table 1 Patient and Disease Characteristics at Baseline for the ITT and *KRAS* Populations

Characteristic	ITT Population, n = 302		*KRAS* Population, n = 180		*KRAS* Population			
					KRAS Wild Type, n = 96		*KRAS* Mutant, n = 84	
	FOLFOX4 With Cetuximab, n = 150	UFOX With Cetuximab, n = 152	FOLFOX4 With Cetuximab, n = 93	UFOX With Cetuximab, n = 87	FOLFOX4 With Cetuximab, n = 56	UFOX With Cetuximab, n = 40	FOLFOX4 With Cetuximab, n = 37	UFOX With Cetuximab, n = 47
Sex, n (%)								
Male	95 (63)	95 (63)	58 (62)	52 (60)	37 (66)	25 (63)	21 (57)	27 (57)
Female	55 (37)	57 (38)	35 (38)	35 (40)	19 (34)	15 (38)	16 (43)	20 (43)
Age, Years								
Median	61.5	60.0	59.0	61.0	56.0	62.0	66.0	59.0
Range	29-84	33-82	38-84	38-77	39-84	39-76	38-76	38-77
Ethnicity, n (%)								
Caucasian	134 (89)	130 (86)	83 (89)	76 (87)	47 (84)	33 (83)	36 (97)	43 (91)
Asian	13 (9)	14 (9)	10 (11)	11 (13)	9 (16)	7 (18)	1 (3)	4 (9)
Hispanic	2 (1)	6 (4)	0	0	0	0	0	0
Other/missing	1 (0.7)	2 (1)	0	0	0	0	0	0
ECOG PS, n (%)								
0	118 (79)	120 (79)	71 (76)	68 (78)	41 (73)	29 (73)	30 (81)	39 (83)
1	29 (19)	30 (20)	20 (22)	19 (22)	13 (23)	11 (28)	7 (19)	8 (17)
2	0	1 (0.7)	0	0	0	0	0	0
Missing	3 (2)	1 (0.7)	2 (2)	0	2 (4)	0	0	0
Primary Tumor Site, n (%)								
Colon	93 (62)	84 (55)	55 (59)	47 (54)	33 (59)	25 (63)	22 (59)	22 (47)
Rectum	54 (36)	66 (43)	35 (38)	39 (45)	21 (38)	15 (38)	14 (38)	24 (51)
Colon and rectum	3 (2)	2 (1)	3 (3)	1 (1)	2 (4)	0	1 (3)	1 (2)
Duration of mCRC, Months								
Median	1.0	0.9	1.1	1.0	1.1	1.0	1.2	1.0
Range	0-41	0-11	0-41	0-11	0-41	0-11	0-19	0-7
Number of Organs Involved, n (%)								
1	64 (43)	59 (39)	37 (40)	36 (41)	24 (43)	14 (35)	13 (35)	22 (47)
2	52 (35)	54 (36)	31 (33)	27 (31)	18 (32)	13 (33)	13 (35)	14 (30)
>2	34 (23)	39 (26)	25 (27)	24 (28)	14 (25)	13 (33)	11 (30)	11 (23)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; FOLFOX4 = 5-fluorouracil, leucovorin and oxaliplatin; ITT = intention-to-treat; mCRC = metastatic colorectal cancer; UFOX = UFT, leucovorin, and oxaliplatin; UFT = tegafur and uracil.

Table 2 Treatment Exposure in the Safety Population

Exposure to Treatment	Safety Population (n =301)	
	FOLFOX4 With Cetuximab (n = 150)	UFOX With Cetuximab (n = 151)
Median Duration of Treatment, Weeks (Q1-Q3)		
UFT	–	23.7 (13.0-32.1)
5-Fluorouracil	25.1 (17.1-34.9)	–
Oxaliplatin	23.9 (16.0-30.0)	22.1 (14.0-28.0)
Cetuximab	24.0 (15.0-33.9)	22.9 (12.1-29.0)
Median Cumulative Dose, mg/m^2 (Q1-Q3)		
Tegafur (n = 115)	–	25,961.1 (17,648.8-39,858.2)
5-Fluorouracil (n = 148)	22,337.5 (14,616.6-29,488.5)	–
Oxaliplatin	844.2 (621.4-1087.3)	832.0 (515.6-1029.9)
Cetuximab	5221.7 (3117.0-7659.5)	5149.8 (2983.1-6747.5)
Relative Dose Intensity of Tegafur, n (%)		
Patients with nonmissing values	–	115 (100)
<60%	–	8 (7)
60%-<80%	–	22 (19)
80%-<90%	–	25 (22)
90%-<120%	–	54 (47)
≥120%	–	6 (5)
Relative Dose Intensity of 5-Fluorouracil, n (%)		
Patients with nonmissing values	148 (100)	–
<60%	5 (3)	–
60%-<80%	56 (38)	–
80%-<90%	31 (21)	–
90%-<120%	56 (38)	–
≥120%	0	–
Relative Dose Intensity of Oxaliplatin, n (%)		
Patients with nonmissing values	148 (100)	151 (100)
<60%	4 (3)	1 (0.7)
60%-<80%	42 (28)	15 (10)
80%-<90%	33 (22)	35 (23)
90%-≤120%	69 (47)	100 (66)
Relative Dose Intensity of Cetuximab, n (%)		
Patients with nonmissing values	144 (100)	148 (100)
<60%	2 (1)	6 (4)
60%-<80%	33 (23)	18 (12)
80%-<90%	37 (26)	25 (17)
90%-≤120%	72 (50)	99 (67)

Abbreviations: FOLFOX4 = 5-fluorouracil, leucovorin and oxaliplatin; Q1-Q3 = interquartile range; UFOX = UFT, leucovorin, and oxaliplatin; UFT = tegafur and uracil.

in the ITT population, with longer PFS, higher response rates, but similar survival for the FOLFOX4 with cetuximab groups compared with the UFOX with cetuximab groups (Table 3; Fig. 2B,C,E, and F). For each treatment arm, patients with *KRAS* wild type tumors had a better prognosis in terms of overall survival, PFS, and best overall response compared with patients with *KRAS* mutant tumors.

Safety

The most common adverse events occurring at any Grade in the safety population in the FOLFOX4 with cetuximab and UFOX with cetuximab groups were skin and subcutaneous tissue disorders (79% vs. 89%, respectively), gastrointestinal disorders (80% vs. 87%), and nervous system disorders (69% vs. 70%). Adverse events ≥ Grade 3 were reported for 80% of patients in the FOLFOX4 with cetuximab group and 72% of patients in the UFOX with cetuximab group. The incidence of adverse events ≥ Grade 3 is summarized according to treatment arm in Table 4. The most frequent were neutropenia (29% vs. 0% respectively), diarrhea (9% vs. 19%), and rash (9% vs. 7%). In relation to composite categories of special interest, the number of patients experiencing Grade 3 acne-like rash (no Grade 4 event occurred) was greater in the FOLFOX4 with cetuximab group compared with the UFOX with cetuximab group (23% vs. 13%), and the incidence of Grade ≥ 3 infusion-related reactions (5% vs. 3%) and cardiac events (0.7% vs. 0.7%) were similar. The safety profiles according to treatment arm of the *KRAS* wild type population were similar to those of the overall safety population (Table 4).

In the FOLFOX4 with cetuximab group and UFOX with cetuximab group, 47% and 40% of patients respectively discontinued study treatment because of adverse events. In the FOLFOX4 with cetuximab group, 5-FU was discontinued because of adverse events in 35 patients (23%), and cetuximab and/or oxaliplatin was discontinued in 64 patients (43%). In the UFOX with cetuximab group, UFT was discontinued because of adverse events in 36 patients (24%), and cetuximab and/or oxaliplatin was discontinued in 47 patients (31%). Both 5-FU/UFT and cetuximab and/or oxaliplatin were discontinued in 22 patients in each treatment group (15%).

In the FOLFOX4 with cetuximab and UFOX with cetuximab groups, the most common adverse events leading to discontinuation of 5-FU or UFT were gastrointestinal disorders (6% vs. 11%, respectively), general disorders/administration site conditions (6% vs. 4%), and skin and subcutaneous tissue disorders (4% vs. 3%). The most common reasons for discontinuation of cetuximab and/or oxaliplatin were nervous system disorders (19% vs. 11%), skin and subcutaneous tissue disorders (8% vs. 5%), and gastrointestinal disorders (5% vs. 7%).

Treatment delays caused by adverse events were more common in the FOLFOX4 with cetuximab (73%) compared with the UFOX with cetuximab (60%) group. The most common adverse events causing delays of study treatment were neutropenia (33% vs. 3%, respectively), diarrhea (5% vs. 20%), thrombocytopenia (12% vs. 9%), and pyrexia (9% vs. 2%). Similar numbers of patients in the FOLFOX4 with cetuximab and UFOX with cetuximab groups had a study treatment dose reduction because of adverse events (39% vs. 34%, respectively): 5-FU or UFT doses were reduced in 34 (23%) and 28 (19%) patients and cetuximab and/or oxaliplatin doses were reduced in 40 (27%) and 35 (23%) patients, respectively.

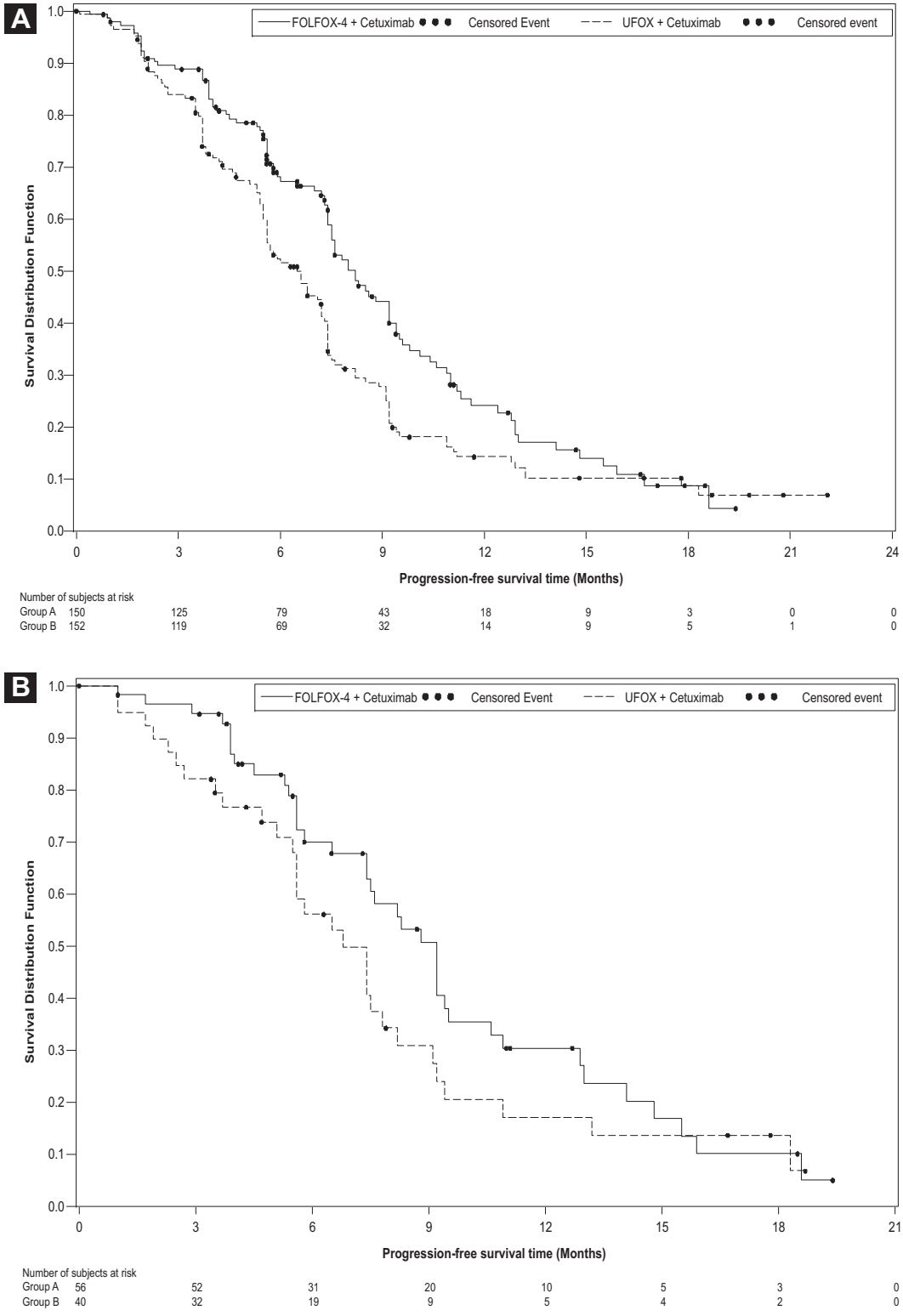
Ten patients in each treatment group (7%) died within 30 days after the last dose of study medication. In the FOLFOX4 with cetuximab and UFOX with cetuximab group, these were because of disease progression in 6 and 5 patients, respectively. Adverse events

Table 3 Efficacy in Intention-to-Treat and *KRAS* Populations

Parameter[a]	Intention-to-Treat		*KRAS* Evaluable		*KRAS* Wild Type		*KRAS* Mutant	
	FOLFOX4 With Cetuximab (n = 150)	UFOX With Cetuximab (n = 152)	FOLFOX4 With Cetuximab (n = 93)	UFOX With Cetuximab (n = 87)	FOLFOX4 With Cetuximab (n = 56)	UFOX With Cetuximab (n = 40)	FOLFOX4 With Cetuximab (n = 37)	UFOX With Cetuximab (n = 47)
Progression-Free Survival								
Median, months (95% CI)	8.2 (7.5-9.2)	6.6 (5.6-7.2)	8.3 (7.5-9.4)	5.7 (5.5-7.2)	9.2 (7.4-9.5)	6.8 (5.6-8.2)	7.6 (7.3-9.6)	5.5 (3.8-6.6)
Hazard ratio (95% CI)	0.68 (0.52-0.89)		0.58 (0.41-0.82)		0.72 (0.44-1.18)		0.32 (0.16-0.63)	
P (log-rank)	0.0048		0.0019		0.1853		0.0005	
Best Response, n (%)								
Complete	3 (2.0)	1 (0.7)	2 (2.2)	0	2 (3.6)	0	0	0
Partial	74 (49.3)	56 (36.8)	50 (53.8)	33 (37.9)	33 (58.9)	21 (52.5)	17 (45.9)	12 (25.5)
Stable disease	51 (34.0)	68 (44.7)	31 (33.3)	38 (43.7)	18 (32.1)	12 (30.0)	13 (35.1)	26 (55.3)
Progressive disease	12 (8.0)	19 (12.5)	5 (5.4)	12 (13.8)	2 (3.6)	4 (10.0)	3 (8.1)	8 (17.0)
Not evaluable	10 (6.7)	8 (5.3)	5 (5.4)	4 (4.6)	1 (1.8)	3 (7.5)	4 (10.8)	1 (2.1)
Response Rate, % (95% CI)	51.3 (43.0-59.6)	37.5 (29.8-45.7)	55.9 (45.2-66.2)	37.9 (27.7-49.0)	62.5 (48.5-75.1)	52.5 (36.1-68.5)	45.9 (29.5-63.1)	25.5 (13.9-40.3)
Odds ratio (95% CI)	1.76 (1.11-2.78)		2.01 (1.12-3.60)		1.45 (0.63-3.30)		2.14 (0.87-5.25)	
P (CMH)	0.0160		0.0175		0.38		0.0870	
Median duration, months (95% CI)	8.7 (7.4-9.6)	5.6 (5.6-7.4)	7.6 (6.3-9.2)	5.6 (4.7-7.3)	8.8 (6.9-12.4)	5.7 (4.4-7.4)	5.7 (5.4-7.9)	5.2 (3.9-7.1)
Survival								
Median, months (95% CI)	18.4 (15.3-20.9)	16.8 (13.9-18.5)	19.5 (15.3-22.5)	18.0 (12.0-20.8)	20.8 (15.8-23.7)	20.1 (13.3-24.8)	14.9 (10.9-20.3)	17.0 (10.2-20.8)
Hazard ratio (95% CI)	0.98 (0.76-1.26)		0.99 (0.71-1.39)		1.09 (0.67-1.78)		0.90 (0.54-1.51)	
P (log-rank)	0.86		0.95		0.73		0.69	

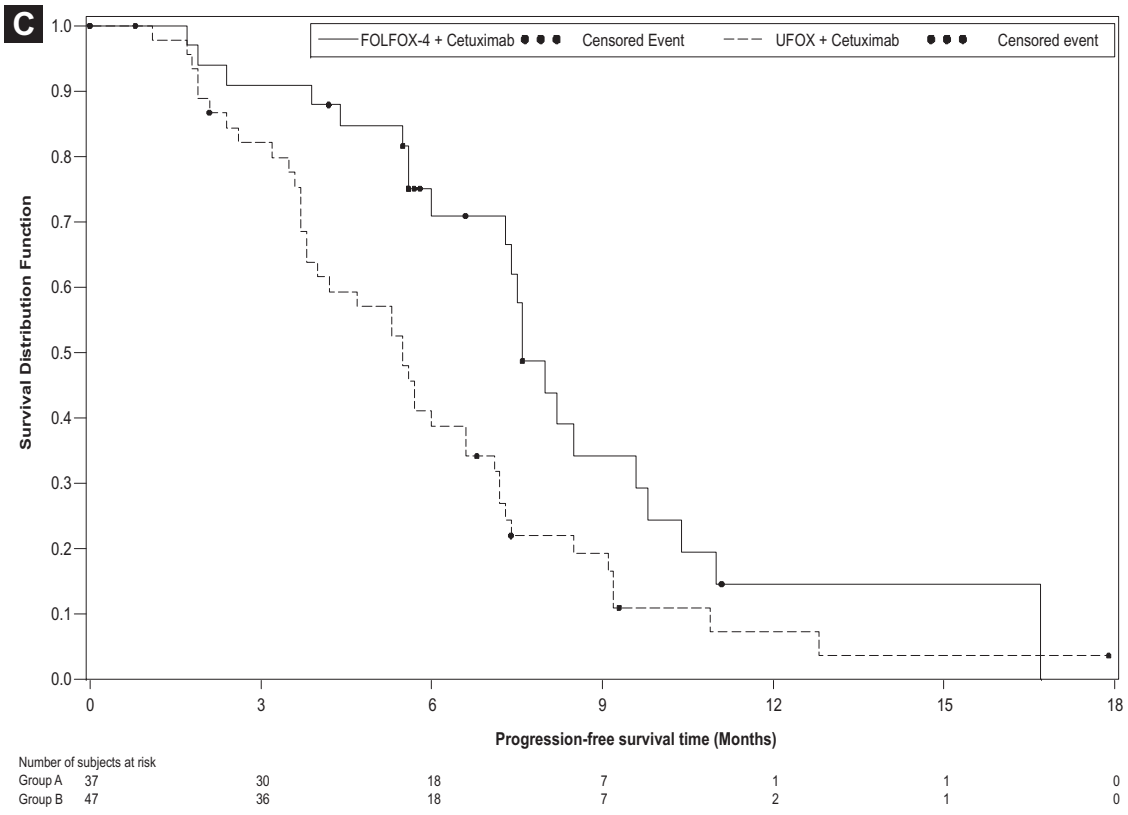
Abbreviations: CMH = Cochran-Mantel-Haenszel; FOLFOX4 = 5-fluorouracil, leucovorin and oxaliplatin; UFOX = UFT, leucovorin, and oxaliplatin; UFT = tegafur and uracil.
[a]Hazard ratios, stratified according to Köhne's criteria, and odds ratios are for FOLFOX4 with cetuximab vs. UFOX with cetuximab. CMH and log-rank tests were also stratified according to Köhne's criteria. Progression-free survival and response were analyzed according to the clinical cutoff date of June 30, 2009; survival data were analyzed using a later cutoff date of August 31, 2011.

Figure 2 Progression-Free and Overall Survival. Kaplan-Meier Plots for Progression-Free (A-C) (Clinical Cutoff June 30, 2009) and Overall Survival (D-F) (Clinical Cutoff August 31, 2011) in the Intention-to-Treat (A) and (D), *KRAS* Wild Type (B) and (E), and *KRAS* Mutant Populations (C) and (F). Group A, FOLFOX4 With Cetuximab; Group B, UFOX With Cetuximab



Abbreviations: FOLFOX4 = 5-fluorouracil, leucovorin and oxaliplatin; UFOX = UFT, leucovorin, and oxaliplatin; UFT = tegafur and uracil.

Figure 2 (continued)



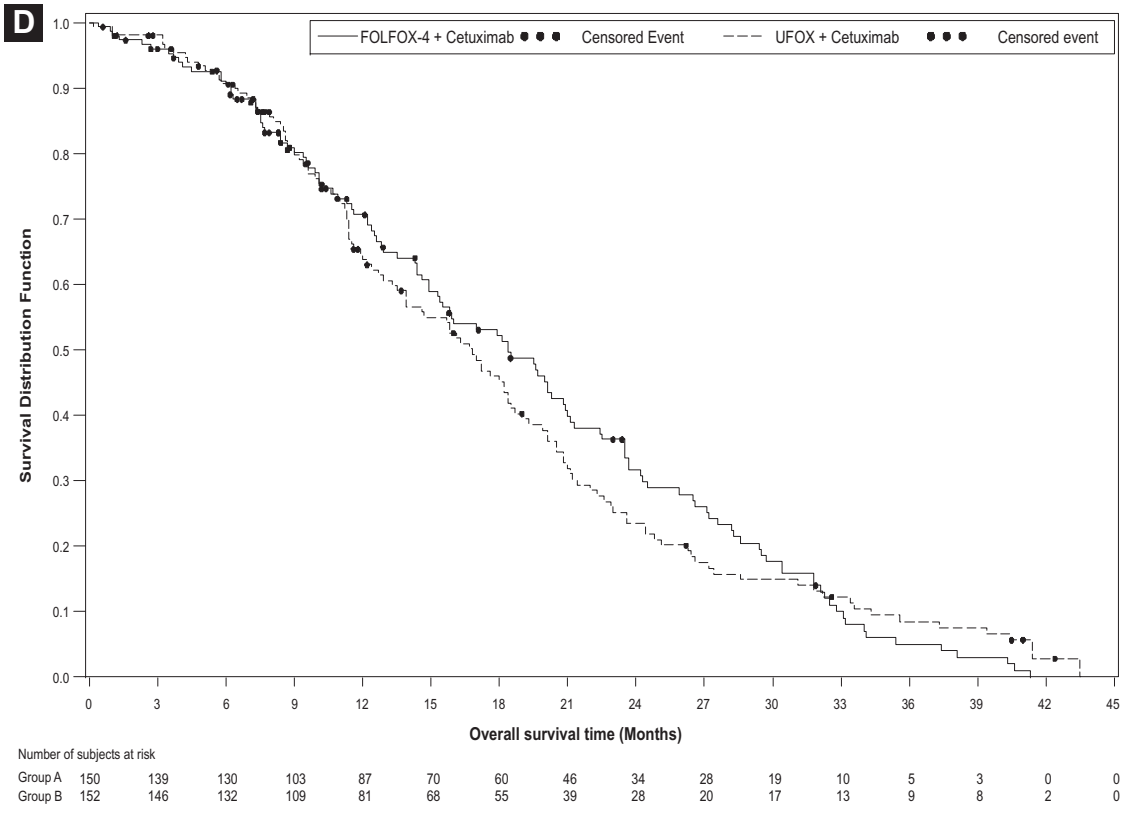
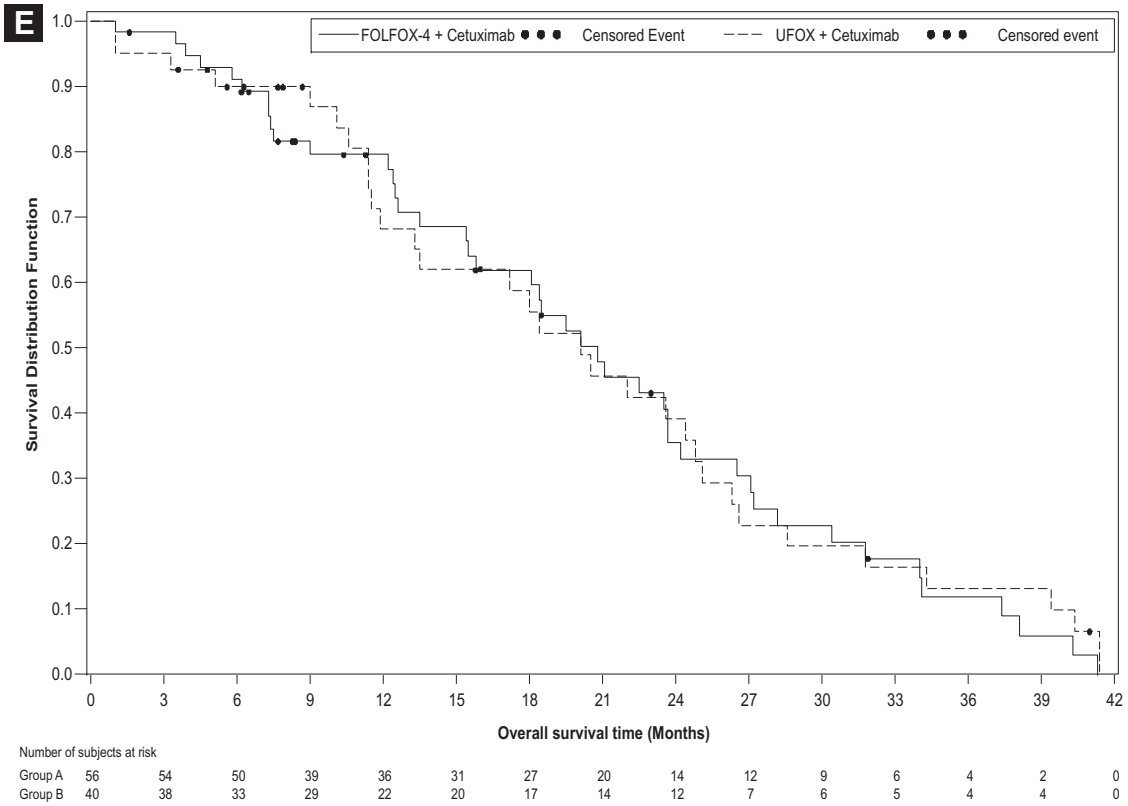


Figure 2 (continued)



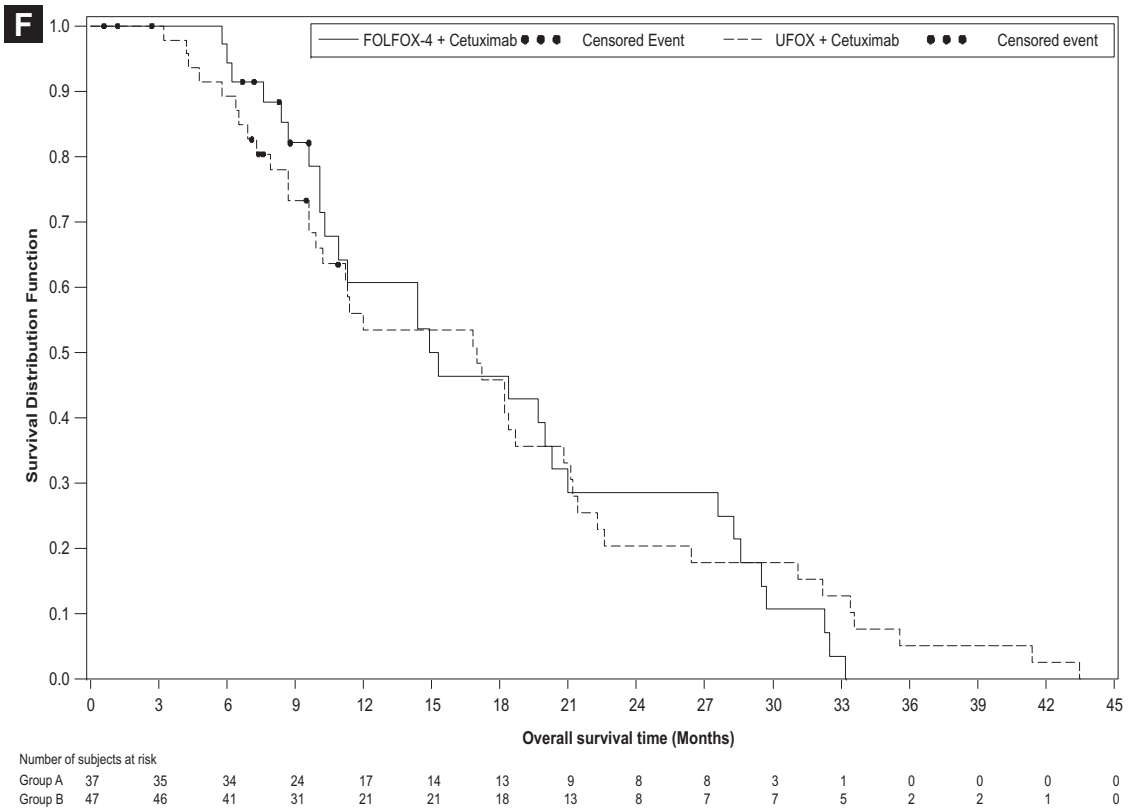


Table 4 Grade ≥ 3 Adverse Events[a] in the Safety and *KRAS* Wild Type Populations

Adverse Event, n (%)	Safety (n = 301)		Safety: *KRAS* Wild Type (n = 96)	
	FOLFOX4 With Cetuximab (n = 150)	UFOX With Cetuximab (n = 151)	FOLFOX4 With Cetuximab (n = 56)	UFOX With Cetuximab (n = 40)
Any Grade 3-5 Event	120 (80)	108 (72)	45 (80)	27 (68)
Neutropenia	43 (29)	0	16 (29)	0
Diarrhea	14 (9)	29 (19)	5 (9)	10 (25)
Rash	14 (9)	10 (7)	8 (14)	2 (5)
Dermatitis Acneiform	12 (8)	5 (3)	6 (11)	1 (3)
Hypokalemia	5 (3)	11 (7)	3 (5)	1 (3)
Vomiting	5 (3)	10 (7)	2 (4)	1 (3)
Leukopenia	9 (6)	0	4 (7)	0
Fatigue	8 (5)	1 (0.7)	3 (5)	1 (3)
Peripheral Sensory Neuropathy	7 (5)	7 (5)	5 (9)	3 (8)
Paronychia	7 (5)	6 (4)	2 (4)	1 (3)
Neuropathy Peripheral	5 (3)	7 (5)	3 (5)	1 (3)
Abdominal Pain	2 (1)	7 (5)	1 (2)	2 (5)
Composite Categories[b]				
Acne-like rash	35 (23)	19 (13)	16 (29)	3 (8)
Infusion-related reaction	7 (5)	5 (3)	2 (4)	2 (5)
Cardiac event	1 (0.7)	1 (0.7)	0	0

Abbreviations: FOLFOX4 = 5-fluorouracil, leucovorin and oxaliplatin; MedDRA = Medical Dictionary for Regulatory Activities; UFOX = UFT, leucovorin, and oxaliplatin; UFT = tegafur and uracil.
[a]Occurring in ≥ 5% of patients of either treatment arm of the safety population according to MedDRA preferred terms and according to composite categories of special interest.
[b]MedDRA preferred terms included in composite categories of special interest are as follows: acne-like rash; acne, acne pustular, dermatitis acneiform, dry skin, erythema, folliculitis, pruritus, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin hyperpigmentation, telangiectasia and xerosis; infusion-related reaction; and cardiac event, as previously defined.[5]

led to death in 4 and 5 patients, respectively. Two deaths, 1 in each arm, were deemed to be related to study treatment: 1 patient in the FOLFOX4 with cetuximab group developed fatal thrombocytopenia and neutropenia that was judged to be related to 5-FU and oxaliplatin; 1 patient in the UFOX with cetuximab group developed diarrhea, loss of appetite, and acute renal failure, resulting in death that was judged to be related to UFT.

Discussion

The initial aim of the current study was to investigate, in a randomized phase II setting, whether oral UFT/LV might be a potential replacement for 5-FUCI/LV as the fluoropyrimidine component of oxaliplatin—cetuximab-based first-line treatment for mCRC. It was anticipated that the study data would be informative as to whether evaluation of the UFOX with cetuximab regimen in a subsequent phase III study was warranted. At the time of study design, the strong predictive significance of *KRAS* mutation status for patients receiving cetuximab was not known and so patients were enrolled without reference to this biomarker. Retrospective analyses of randomized studies subsequently indicated that the benefit associated with the addition of cetuximab to chemotherapy was limited to patients with *KRAS* exon 2 wild type tumors.[25,26] A decision was consequently taken by the lead investigator and study sponsor to curtail all recruitment to the current study from June 30, 2008. At this time, 302 of the planned 420 patients had been enrolled. This report describes outcome according to the protocol-defined populations and end points in patients enrolled before this date. A further exploratory analysis of outcome in patient subgroups defined by *KRAS* tumor mutation status is also included.

The treatment arms of the ITT population were essentially balanced with respect to baseline patient and disease characteristics. Treatment exposure measured according to relative dose intensities for 5-FU/tegafur, oxaliplatin, and cetuximab in the safety population marginally favored the UFOX with cetuximab over the FOLFOX4 with cetuximab group for each agent. However, it should be noted that because of a fault in the case report forms, reliable data were available for tegafur dosing from only a subset of 115 of 151 patients (76%). The baseline characteristics of this subset did not appear to differ substantially from the ITT population and they are therefore likely to be representative of the overall group.

In the primary efficacy analysis of the ITT population, PFS was shown to be significantly longer in patients in the FOLFOX4 with cetuximab group compared with UFOX with cetuximab group (HR, 0.68; 95% CI, 0.52-0.89; $P = .0048$). This difference did not appear to be related to treatment exposure, which tended to favor the UFOX with cetuximab group, or to any imbalance in baseline characteristics. The median PFS time for the FOLFOX4 with cetuximab group in the current study (8.2 months) was similar to that reported for the corresponding ITT population of the Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer (OPUS) study (7.2 months).[5] The odds for response were also greater in the FOLFOX4 with cetuximab group compared with the UFOX with cetuximab group. However, no clear difference in overall survival time was demonstrated between the treatment

groups (stratified HR, 0.98; 95% CI, 0.76-1.26; $P = .86$). Median overall survival time was comparable for the FOLFOX4 with cetuximab group of the current study (18.4 months) and the corresponding ITT population of the OPUS study (18.3 months).[5] The administration of chemotherapy after the study was essentially balanced between the treatment groups and consequently does not explain the apparent discrepancy between the treatment groups for PFS and overall survival outcomes.

Updated analyses of the OPUS and Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) studies confirmed that the clinical activity of cetuximab in combination with chemotherapy as first-line treatment for mCRC could only be demonstrated unequivocally in patients with *KRAS* wild type tumors.[5,7] Furthermore, for OPUS study patients whose tumors carried a *KRAS* mutation, PFS and response rate were significantly decreased and a trend for shorter overall survival was observed when cetuximab was added to FOLFOX4.[5,27] A similar negative effect in patients with *KRAS* mutant tumors was also reported for another EGFR antibody, panitumumab, in combination with FOLFOX4.[6] In view of the effect of the tumor *KRAS* mutation status in patients with mCRC receiving cetuximab, an exploratory analysis of treatment outcome in the FUTURE study of *KRAS* subgroups was carried out. Although the availability of a tumor biopsy or archived tumor sample was an eligibility requirement, evaluable specimens were only obtained from 180 of 302 patients (60%) of the ITT population. Because of the limited sample size of the *KRAS* subgroups, caution should be exercised in the interpretation of the results.

Efficacy outcomes according to treatment in the overall *KRAS* evaluable population and the *KRAS* wild type and *KRAS* mutant subgroups were found to be broadly comparable with those of the ITT population, with longer PFS and higher response rates in the FOLFOX4 with cetuximab groups compared with the UFOX with cetuximab groups but similar overall survival times. Considering the known characteristics of cetuximab activity, clinical practice, and current regulatory approval, of particular interest was outcome in patients with *KRAS* wild type tumors. Although PFS time was longer and the best overall response rate higher in the FOLFOX4 with cetuximab group compared with the UFOX with cetuximab group, median overall survival times were similar and in excess of 20 months in both treatment groups. In relation to PFS, as suggested in subgroup analysis of the Combination Chemotherapy With or Without Cetuximab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer (COIN) study,[28,29] in the Arbeitsgemeinschaft Internistische Onkologie (AIO) KRK-0104 study,[30] and in line with a recent meta-analysis,[31] these data are broadly consistent with the superiority of the infusional administration of 5-FU compared with the oral administration of fluoropyrimidine in patients with *KRAS* wild type mCRC who receive first-line oxaliplatin-based chemotherapy combinations including cetuximab.

The prognosis for best overall response, PFS, and overall survival was essentially better in the *KRAS* wild type groups compared with the *KRAS* mutant groups of both treatment arms. Such outcomes might be expected to be a consequence of positive effects associated with the addition of cetuximab to chemotherapy in the *KRAS* wild type groups and negative effects in the *KRAS* mutant groups.

The side effect profiles of FOLFOX4 with cetuximab and UFOX with cetuximab were manageable and consistent with the known profiles of the individual agents. In the safety population, Grade $\geq$ 3 adverse events were reported marginally more frequently in the FOLFOX4 with cetuximab group compared with the UFOX with cetuximab group (80% vs. 72%, respectively). In relation to particular Grade $\geq$ 3 adverse events, hematological toxicity appeared to be higher in the FOLFOX4 with cetuximab group in particular in relation to neutropenia (29% vs. 0%), and diarrhea, a side effect known to be associated with UFT administration,[10] was more common in the UFOX with cetuximab group (9% vs. 19%). Grade 3 acne-like rash was more common in the FOLFOX4 with cetuximab group (23% vs. 13%). The occurrence and severity of acne-like rash or skin reactions has previously been reported to be associated with cetuximab efficacy in a number of mCRC studies.[32-35] Incidence data for Grade $\geq$ 3 adverse events in the *KRAS* wild type population were comparable with those for the safety population.

Conclusion

This exploratory study has demonstrated that in the first-line treatment of patients with mCRC, the combination of UFOX with cetuximab had an acceptable safety profile but inferior antitumor activity in relation to PFS and response compared with FOLFOX4 with cetuximab. The 2 regimens were comparable in relation to overall survival. These efficacy data, which are similar to those for the oral fluoropyrimidine capecitabine in the COIN study, indicate that UFT should not be used in combination with oxaliplatin and cetuximab as first-line treatment for mCRC.

Clinical Practice Points

- Infusional 5-FU/LV remains a key component of chemotherapy combinations, including FOLFOX4, used in the first-line treatment of mCRC.
- In an attempt to maximize patient benefit by minimizing toxicity and the inconvenience of prolonged continuous infusion, orally deliverable prodrugs of 5-FU, including tegafur, a component of UFT, have been developed.
- This randomized phase II study was designed to assess the efficacy and safety of FOLFOX4 in combination with the EGFR antibody, cetuximab, compared with UFOX with cetuximab as a first-line treatment for mCRC.
- Patients were enrolled without consideration of their tumor *KRAS* mutation status. During the course of the study, and resulting subsequently in curtailment of enrollment, it was reported that the activity of cetuximab was limited to patients with *KRAS* wild type tumors.
- In the primary ITT analysis, PFS was significantly longer in the FOLFOX4 with cetuximab group compared with the UFOX with cetuximab group (HR, 0.68; 95% CI, 0.52-0.89; $P = .0048$).
- The response rate was also significantly higher in the FOLFOX4 with cetuximab group, although outcomes for overall survival were comparable.
- A similar pattern in efficacy outcomes was seen in patients with *KRAS* wild type tumors, the subgroup including those likely to benefit from the addition of cetuximab to chemotherapy.

- The safety profile of UFOX with cetuximab was manageable and consistent with the known side effects of the individual agents.
- UFT should not be used in combination with oxaliplatin and cetuximab as first-line treatment for mCRC.

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Disclosure

J.-Y.D. reports speaking at symposia for, an advisory role with, and has received research funding from Merck Serono; C.B. reports speaking at symposia for Merck Serono, Italy, Roche, and Amgen, and an advisory role with Merck Serono, Italy, and Amgen; M.S. is an employee of Merck KGaA; J.H., an employee of Cancer Communications and Consultancy Ltd (Knutsford, UK) provided medical writing services, which were funded by Merck KGaA, Darmstadt, Germany; these included initial drafting of the manuscript and modification of the draft in accordance with guidance from other authors; S.P.E. is an employee of Merck Serono, UK; all other authors state that they have no conflicts of interest.

References

1. Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005; 23:4866-75.
2. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18:2938-47.
3. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; 355:1041-7.
4. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; 22:229-37.
5. Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol* 2011; 22:1535-46.
6. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010; 28:4697-705.
7. Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011; 29:2011-9.
8. Borner MM, Schoffski P, de Wit R, et al. Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. *Eur J Cancer* 2002; 38:349-58.
9. Bennouna J, Saunders M, Douillard JY. The role of UFT in metastatic colorectal cancer. *Oncology* 2009; 76:301-10.
10. Malet-Martino M, Martino R. Clinical studies of three oral prodrugs of 5-fluorouracil (capecitabine, UFT, S-1): a review. *Oncologist* 2002; 7:288-323.
11. Omura K. Clinical implications of dihydropyrimidine dehydrogenase (DPD) activity in 5-FU-based chemotherapy: mutations in the DPD gene, and DPD inhibitory fluoropyrimidines. *Int J Clin Oncol* 2003; 8:132-8.
12. Cao S, Frank C, Shirasaka T, et al. 5-Fluorouracil prodrug: role of anabolic and catabolic pathway modulation in therapy of colorectal cancer. *Clin Cancer Res* 1995; 1:839-45.
13. Okabe H, Toko T, Saito H, et al. Augmentation of the chemotherapeutic effectiveness of UFT, a combination of tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] with uracil, by oral l-leucovorin. *Anticancer Res* 1997; 17:157-64.
14. Rustum YM. Mechanism-based improvement in the therapeutic selectivity of 5-FU prodrug alone and under conditions of metabolic modulation. *Oncology* 1997; 54(suppl 1):7-11.
15. Douillard JY, Hoff PM, Skillings JR, et al. Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2002; 20:3605-16.
16. Carmichael J, Popiela T, Radstone D, et al. Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2002; 20:3617-27.
17. Bajetta E, Di Bartolomeo M, Buzzoni R, et al. Uracil/ftorafur/leucovorin combined with irinotecan (TEGAFIRI) or oxaliplatin (TEGAFOX) as first-line treatment for metastatic colorectal cancer patients: results of randomised phase II study. *Br J Cancer* 2007; 96:439-44.
18. Bennouna J, Perrier H, Paillot B, et al. A phase II study of oral uracil/ftorafur (UFT) plus leucovorin combined with oxaliplatin (TEGAFOX) as first-line treatment in patients with metastatic colorectal cancer. *Br J Cancer* 2006; 94:69-73.
19. Feliu J, Vicent JM, Garcia-Giron C, et al. Phase II study of UFT and oxaliplatin in first-line treatment of advanced colorectal cancer. *Br J Cancer* 2004; 91:1758-62.
20. Kim K, Nam E, Lee NS, et al. Oxaliplatin and UFT combination chemotherapy in patients with metastatic colorectal cancer. *Am J Clin Oncol* 2002; 25:354-7.
21. Rosati G, Cordio S, Tucci A, et al. Phase II trial of oxaliplatin and tegafur/uracil and oral folinic acid for advanced or metastatic colorectal cancer in elderly patients. *Oncology* 2005; 69:122-9.
22. Tabernero J, Van Cutsem E, Diaz-Rubio E, et al. Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2007; 25:5225-32.
23. Kohne CH, Cunningham D, Di CF, et al. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol* 2002; 13:308-17.
24. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92:205-16.
25. Bokemeyer C, Bondarenko I, Hartmann JT, et al. KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: the OPUS experience. *J Clin Oncol* 2008; 26 (abstract 4000).
26. Van Cutsem E, Lang I, D'haens G, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: the CRYSTAL experience. *J Clin Oncol* 2008; 26 (abstract 2).
27. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009; 27:663-71.
28. Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011; 377:2103-14.
29. Madi A, Fisher D, Wilson RH, et al. Oxaliplatin/capecitabine vs oxaliplatin/infusional 5-FU in advanced colorectal cancer: the MRC COIN trial. *Br J Cancer* 2012; 107:1037-43.
30. Moosmann N, von Weikersthal LF, Vehling-Kaiser U, et al. Cetuximab plus capecitabine and irinotecan compared with cetuximab plus capecitabine and oxaliplatin as first-line treatment for patients with metastatic colorectal cancer: AIO KRK-0104—a randomized trial of the German AIO CRC study group. *J Clin Oncol* 2011; 29:1050-8.
31. Ku GY, Haaland BA, de Lima Lopes G Jr. Cetuximab in the first-line treatment of K-ras wild-type metastatic colorectal cancer: the choice and schedule of fluoropyrimidine matters. *Cancer Chemother Pharmacol* 2012; 70:231-8.
32. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351:337-45.
33. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med* 2007; 357:2040-8.
34. Saltz LB, Meropol NJ, Loehrer PJ Sr., et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 2004; 22:1201-8.
35. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; 360:1408-17.

Supplemental Table 1	Anticancer Therapy During the Follow-Up Period in the Intention-To-Treat Population	
Treatment, n (%)[a]	FOLFOX4 With Cetuximab (n = 150)	UFOX With Cetuximab (n = 152)
Any	98 (65)	102 (67)
Chemotherapy	97 (65)	97 (64)
Immunotherapy	23 (15)	24 (16)
Radiotherapy	10 (7)	15 (10)
Surgery	10 (7)	7 (5)
Hormonal	0	1 (0.7)
Other	26 (17)	23 (15)

Abbreviations: FOLFOX4 = 5-fluorouracil, leucovorin and oxaliplatin; UFOX = UFT, leucovorin, and oxaliplatin; UFT = tegafur and uracil.
[a]Patients might have received more than 1 type of anticancer therapy.