

Cetuximab in combination with weekly 5-fluorouracil/folinic acid and oxaliplatin (FUFOX) in untreated patients with advanced colorectal cancer: a phase Ib/II study of the AIO GI Group

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Background: This two-part phase Ib/II study investigated the feasibility of administering cetuximab in combination with oxaliplatin and infusional 5-fluorouracil (5-FU)/folinic acid (FA) in a weekly schedule (AIO FUFOX protocol) as first-line treatment in patients with epidermal growth factor receptor-detectable advanced colorectal cancer.

Patients and methods: Cetuximab was administered weekly: 400 mg/m² initial dose, then 250 mg/m² and FUFOX: oxaliplatin 50 mg/m², FA 500 mg/m² and 5-FU as a 24-h infusion at either 1500 or 2000 mg/m² administered for 4 weeks followed by a 1-week rest (one cycle).

Results: Dose-limiting toxicity (grade 3 diarrhea) occurred in 3 of 14 assessable patients receiving 5-FU at standard 2000 mg/m². This dose was administered to a further 25 patients. Cetuximab combined with FUFOX was generally well tolerated with the most common grade 3/4 adverse events being diarrhea (27%) and paresthesia (16%). The confirmed response rate for patients receiving 5-FU at standard 2000 mg/m² (N = 41) was 56%, with a median duration of 9.3 months. Median progression-free and overall survival times including all 49 patients were 8.1 (95% confidence interval 6.0–9.7) and 28.2 months, respectively. Cetuximab pharmacokinetics seemed not to be different for combination with FUFOX compared with cetuximab/irinotecan combinations.

Conclusion: This protocol is well tolerated and shows promising efficacy supporting further investigation.

Key words: ACRC, cetuximab, EGFR, first-line chemotherapy, FUFOX, oxaliplatin

introduction

Colorectal cancer (CRC) accounts for >500 000 deaths annually worldwide [1]. There are currently three active cytotoxic agents that have been shown to be effective in the treatment of advanced colorectal cancer (ACRC): 5-fluorouracil combined with folinic acid (5-FU/FA), irinotecan and oxaliplatin. Compared with best supportive care (BSC) alone, the use of sequential combined regimens can improve median survival times for ACRC patients from 6–9 months [2] to >20 months [3, 4]. The cytotoxic regimens of FOLFOX (oxaliplatin every 2 weeks plus infusional 5-FU/FA) and FOLFIRI (irinotecan every 2 weeks plus infusional 5-FU/FA) have both been approved in

this setting in Europe and the United States and may be essentially equivalent in terms of efficacy [3, 5].

Recent anticancer drug development has focused on agents targeting molecules that are expressed strongly or exclusively by the tumor cell such as the epidermal growth factor receptor (EGFR), which is expressed by most CRCs [6–10]. Cetuximab (Erbix®) is a therapeutic immunoglobulin G1 mAb that specifically targets EGFR [11, 12]. In combination with irinotecan, cetuximab is approved for the treatment of EGFR-expressing ACRC that has failed prior irinotecan-based therapy. Several clinical studies are exploring the use of cetuximab combined with irinotecan and 5-FU/FA [8, 13, 14] or oxaliplatin and 5-FU/FA [15, 16] in the first-line setting.

FUFOX is a once-weekly oxaliplatin (50 mg/m²) plus infusional 5-FU/FA regimen that has been shown to have superior efficacy and less toxicity than the bolus 5-FU/FA Mayo Clinic regimen in patients with ACRC [17]. The primary objective of the current study was to explore the feasibility of

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administering cetuximab in combination with FUFOX at their recommended doses. However, as this was the first study investigating this particular combination, and recognizing that both cetuximab [18] and infusional 5-FU [19] have previously been associated with mucocutaneous toxicity and diarrhea, an initial 5-FU dose selection phase (1500 mg/m² versus standard 2000 mg/m²) was planned at the beginning of the trial to decrease the toxicity risk for participating patients.

patients and methods

main eligibility criteria

Patients with histologically confirmed ACRC were eligible for inclusion if they were ≥18 years of age; had adequate hematological, hepatic and renal function; an Eastern Cooperative Oncology Group performance status two or less and had at least one bidimensionally measurable indicator lesion outside an irradiated area. The primary tumor or at least one metastasis had to show evidence of EGFR expression. Patients were ineligible if they had undergone surgery within 4 weeks before study entry or had documented or symptomatic brain metastases or previous exposure to mAbs, signal transduction inhibitors or EGFR-targeted therapy. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All subjects provided informed consent, both verbally and in writing.

trial design

This was a multicenter, single-arm phase Ib/II study. Enrollment of subjects with EGFR-expressing ACRC was conducted at six centers in Germany and two in Austria. Tumor EGFR expression was evaluated centrally, by immunohistochemistry. To minimize the risk of unacceptable toxicity, the study was split into two parts (I and II). In part I, safety and pharmacokinetic (PK) data were collected. Part I was subdivided into phase A, during which the most appropriate dose of 5-FU (1500 mg/m² or standard 2000 mg/m²) was selected, on the basis of the occurrence during the first 5 weeks of treatment of predefined dose-limiting toxic effects (DLTs; Table 1) and phase B, during which patients receiving a therapeutic benefit continued on their treatment. In part I, phase A, the first six patients were to receive 5-FU at 1500 mg/m². On the basis of the number of DLTs observed, six additional patients were to be treated at this (if three or four of six patients experienced a DLT) or the higher 5-FU dose level (if zero to two of the first six patients experienced a DLT). If one or two of the patients treated at standard 2000 mg/m² subsequently experienced a DLT, a further six were treated at this dose level. If three or more of the first six patients treated at the higher standard 2000 mg/m² dose level experienced DLTs, a further six were recruited into the 1500 mg/m² group. Following the treatment of the last recruited patient, a final dose for 5-FU was selected. During part II, a larger number of patients were treated at this selected dose, in order to assess the efficacy and safety of the cetuximab/FUFOX combination. Patients from part I who had received the unselected dose were allowed to change to the selected dose at this time. During part II, the original DLT definitions were used to designate adverse events (AEs) of special interest. It was anticipated that a total of 40 patients would receive the FUFOX regimen incorporating the selected 5-FU dose.

Cycles lasted for 5 weeks, with cetuximab administered each week at the standard dose of 400 mg/m² on week 1, with subsequent weekly infusions of 250 mg/m² and followed by weekly FUFOX, administered for 4 consecutive weeks followed by a 1-week rest period, comprising oxaliplatin (50 mg/m² infused over 2 h), FA (500 mg/m² as a 2-h infusion, either 1 h after or at the same time as oxaliplatin) and 5-FU as a 24-h infusion at either 1500 mg/m² or standard 2000 mg/m². Treatment was

Table 1. Predefined dose-limiting toxic effects

Dose-limiting toxic effects ^a	Grade
Preferred term	
Leucopenia or neutropenia	Grade 4 (for ≥7 days)
Leucopenia or neutropenia with complications (e.g. fever, infection)	Grade 3 or 4
Thrombopenia	Grade 3 (for ≥7 days) or grade 4
Diarrhea	Grade 3
Mucositis	Grade 3 or 4
Hepatic toxicity	Grade 3 ^b or grade 4
Acute neuropathy	Grade 3 or 4
Skin toxicity	Grade 4
Vomiting	Grade 4
Other organ toxicity	>Grade 2 ^c
Criteria	
Any toxicity requiring cetuximab and/or chemotherapy delay for >2 weeks	

^aDose-limiting toxicity was defined as the occurrence of at least one of the above, during phase A of part I of the study, according to National Cancer Institute—Common Toxicity Criteria version 2.0.

^bExcept in the case of liver metastasis.

^cExcluding medically irrelevant side-effects (e.g. hair loss, altered taste) and allergic reactions to cetuximab or chemotherapy.

continued until the occurrence of progressive disease (PD) or unacceptable toxicity.

If a patient experienced grade 4 skin toxicity, cetuximab was discontinued. In the event of grade 3 skin toxicity, cetuximab therapy could have been delayed for up to two consecutive infusions during phase A (up to four consecutive infusions for phase B and part II) with no change in the dose level. In the event of a second or third occurrence of grade 3 skin toxicity, cetuximab therapy could be delayed again for up to two consecutive weeks during phase A (up to four consecutive infusions for phase B and part II) with concomitant dose reductions to 200 and 150 mg/m², respectively. Cetuximab dose reductions were permanent. Cetuximab was to be discontinued if more than two consecutive infusions were withheld during phase A (more than four consecutive infusions withheld during phase B or part II) or if there was a subsequent occurrence of grade 3 skin toxicity despite appropriate dose reductions.

The primary objective was to investigate the safety of the combination of cetuximab plus oxaliplatin plus 5-FU/FA as determined by the frequency of DLTs and AEs occurring during the dose selection part of the study. Secondary objectives included assessments of the safety of the selected regimen in 40 patients; the PK of cetuximab; the overall response rate (confirmed response, requiring a repeat consecutive assessment after a minimum of 4 weeks from the first, with study evaluations taking place at baseline, before the second cycle, then every two cycles, with each cycle lasting 5 weeks); duration of response (DOR); progression-free survival (PFS) time and overall survival (OS) time.

PK analysis

During phase A of part I, blood samples (2.5 ml) were collected at the following times: day 1, before infusion of cetuximab and 2 h after start of infusion; day 8 and day 15, before infusion of cetuximab; day 22, before infusion of cetuximab and 1, 2, 5, 24, 48 and 96 (or at the discretion of the investigator at 72) h after the start of infusion; day 29, before infusion of cetuximab. In phase B of part I, blood samples were taken during each

subsequent cycle, before each cetuximab infusion. This sampling regimen was also used for the first 10 subjects in part II. For the remainder, one blood sample was taken at each cycle, before each infusion of cetuximab. At the end of study visit, a serum sample was taken and used to assess both the serum concentration of cetuximab and the presence of human antichimeric antibodies.

statistical methods and considerations

The intention to treat (ITT) population was identical with the safety population and comprised all subjects who received any dose of cetuximab. The DLT population comprised all subjects who completed the first 5 weeks of treatment or who stopped treatment because of DLT during that time. An assessment of disease status and toxicity/AEs was carried out at each visit. AEs were graded according to the toxicity criteria defined in the National Cancer Institute—Common Toxicity Criteria, version 2.0.

The primary objective was addressed using data gained during the first cycle of treatment (phase A), with the primary variable being the occurrence of DLT (as defined in Table 1) or AEs. Other safety analyses were carried out using data collected after phase A and before the clinical data cut-off of 01 April 2005. For the OS analysis, follow-up continued until 30 June 2006 (all patient data included).

Summary statistics on time-to-event variables were calculated according to Kaplan–Meier methods [20]. The PFS time of patients without disease progression before the end of the study was censored at the last on-study tumor assessment date at which the patient was considered to be progression free. PFS was defined as the number of days between the first administration of cetuximab and the first on-study assessment of PD or death within 105 days after the last tumor assessment or first administration of cetuximab; DOR was defined as the time from first assessment of complete or partial response until the first date of PD or death, when observed within 105 days after the last response assessment. Deaths were evaluated as progression if they occurred at any time on study or within 105 days after the last on-study tumor assessment. Patients without disease progression who discontinued the study for any reason were censored at the last on-study tumor assessment date.

Treatment of 6–12 patients at each of the 5-FU dose levels was considered to be sufficient to select the 5-FU dose for part II of the study. Treatment of 40 patients at the selected 5-FU dose level was considered to be sufficient to meet the primary safety objective of the study. Sample size was therefore fixed without test power considerations.

results

patient demographics

Of 79 ACRC patients screened, 72 (91%) had EGFR-expressing tumors and 49 patients fulfilled all entry criteria, provided informed consent and were enrolled. The first patient entered the study on 23 April 2003 and the last on 03 March 2004. Twenty-four subjects entered part I: eight patients rather than a planned six were scheduled to receive 5-FU at 1500 mg/m² (as two additional patients had provided informed consent after the end of recruitment was announced) and 16 were scheduled to receive standard 2000 mg/m² (Figure 1). Twenty-five subjects were subsequently enrolled into part II of the study. Baseline characteristics are detailed in Table 2.

5-FU dose selection

Of the eight patients who received 5-FU at 1500 mg/m², one discontinued treatment due to a grade 3 infusion-related reaction at the first cetuximab infusion. Of the seven remaining

patients comprising the DLT population at this dose level, DLT was reported for one patient (grade 3 diarrhea, thrombosis and thrombophlebitis). Nine patients were subsequently treated at standard 2000 mg/m². As two DLTs were reported in this group (both grade 3 diarrhea), seven additional patients were recruited. One further DLT was reported (grade 3 diarrhea). Three of 14 (DLT population) assessable patients treated at the standard dose level therefore experienced diarrhea as a DLT. There were no study treatment delays of >9 days and no dose reductions during phase A of part I (i.e. the first 5 weeks of study treatment). The 2000 mg/m² regimen was therefore deemed to show an acceptable safety profile and was selected for part II of the study, allowing the administration of both cetuximab and FUFOX at their recommended doses. Consequently, a further 25 patients were recruited and received 5-FU at standard 2000 mg/m², making a total of 41 patients assigned to this dose level.

compliance

The majority of dose reductions and delays for cetuximab and chemotherapy were due to AEs. While 11 patients experienced cetuximab dose reductions, nine as a consequence of AEs (six of nine due to skin toxicity, managed according to predefined criteria), the relative dose intensity for cetuximab was ≥80% in 30 of 49 (61%) patients and between 60% and 80% in a further 14 (29%). Cetuximab infusions were delayed at some time during the study for 38 (78%) patients. In 15 cases (31%), those delays were for 16 days or longer. In 30 instances (61%), delays were a consequence of AEs; most commonly, nasopharyngitis (11 patients, 22%), diarrhea (10 patients, 20%) and skin exfoliation (six patients, 12%). Five patients (10%) continued cetuximab treatment after the discontinuation of FUFOX. Dose reductions of oxaliplatin were necessary for 18 patients (37%) but the relative dose intensity was ≥80% in 34 of 49 (69%) cases and between 60% and 80% for the majority of the remainder. Dose reductions of 5-FU were required for 10 (24%) patients, all in the standard 2000 mg/m² group, with a relative dose intensity of ≥80% in 32 of 49 (65%) patients. The proportion of delays for 16 days or longer was higher for 5-FU (17 of 49, 35% of patients) than for oxaliplatin (11 of 49, 22% of patients).

adverse events

The combined treatment was generally well tolerated. The most common AEs observed at any grade in the ITT/safety population according to System Organ Class categories were skin and subcutaneous system (90%) and gastrointestinal disorders (88%). Grade 3/4 AEs regardless of relationship to study treatment were reported for 40 subjects (82%), seven in the 1500 mg/m² group (88%) and 33 (81%) in the standard 2000 mg/m² group, with 32 patients overall experiencing treatment-related AEs (Table 3). In patients receiving 5-FU at standard 2000 mg/m², diarrhea was the most frequently reported treatment-related grade 3/4 toxicity occurring in 29% of patients. However, it was usually of short duration and manageable and did not result in high rates of dehydration or hospital admission. Oxaliplatin-induced neuropathy was the second most common treatment-related grade 3/4 toxicity in this group (17%); with all grade neurotoxicity-associated AEs

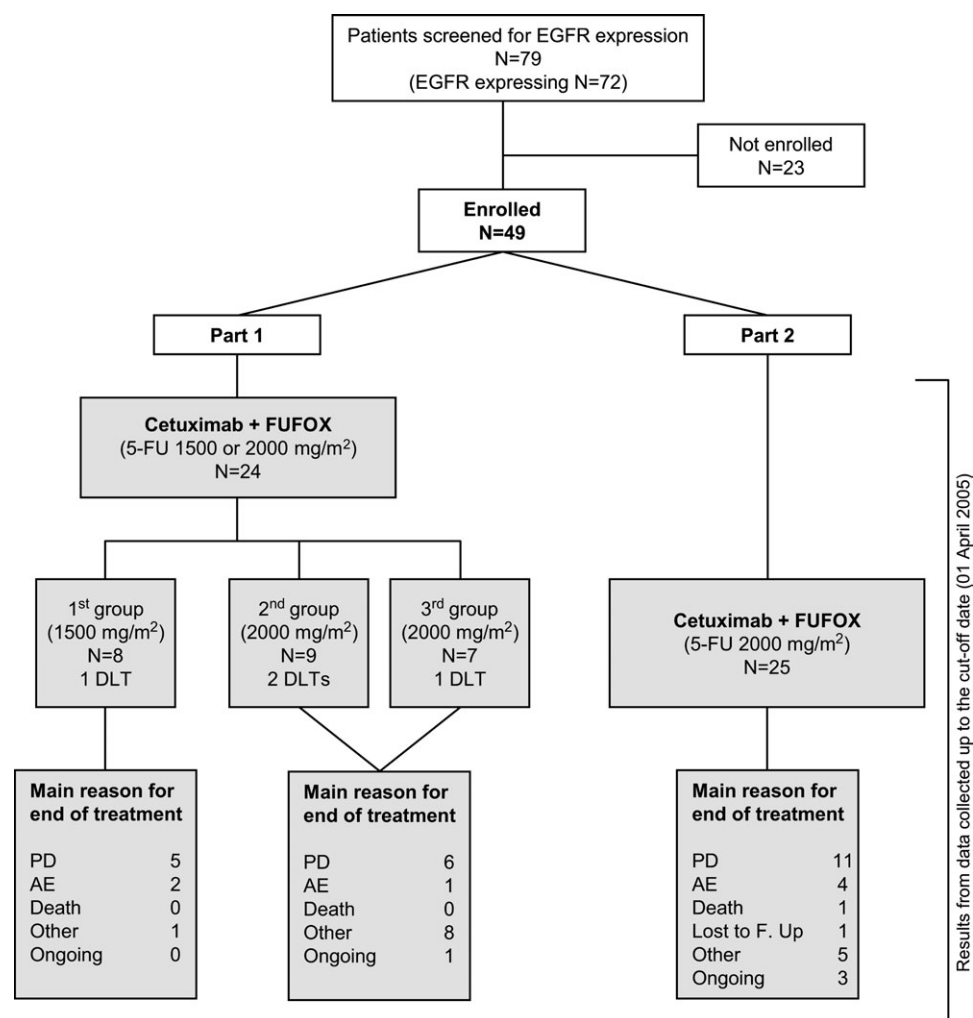


Figure 1. Flow diagram showing number of subjects in each stage of the study (all screened subjects). EGFR, epithelial growth factor receptor; 5-FU, 5-fluorouracil; DLT, dose-limiting toxicity PD, progressive disease; AE, adverse event; F. Up, follow-up.

being reported for 27 (55%) patients in the ITT/safety population. Acne-like rash was reported for 11 patients (22%), all of whom received 5-FU at standard 2000 mg/m² (27% of the patients in this group) but reached grade 3 in only one (2%). Grade 3 infusion-related reactions were noted for three (6% of all) patients. Grade 3 neutropenia occurred in 4% of all patients.

efficacy

Efficacy data are summarized in Table 4. For the standard 2000 mg/m² group of patients (selected dose level), the confirmed response rate, as assessed by the investigators, was 56% with a median DOR of 9.3 months and a disease control rate of 78%. Four patients were lost to follow-up or were not assessable (8%), whereas 14% of patients progressed during their first treatment cycles. The median PFS time for the ITT population (all patients, regardless of dose level) was 8.1 months, with PFS time censored in 16 patients at the clinical cut-off date of 01 April 2005 (Figure 2A). Of these patients, three were still under treatment at this time, six had withdrawn as a consequence of AEs, two due to surgery, four had withdrawn consent and one was erroneously excluded. After a median

follow-up from the end of study visit of 32.4 months, the median OS time (ITT population) was 28.2 months (Figure 2B). Four (8%) patients with initially nonresectable liver metastases had their disease rendered resectable by the cetuximab/FUFOX treatment and subsequently underwent surgery (R0 resections in two).

Poststudy salvage treatment was administered to 31 (63%) patients, with 22 of those patients receiving one to three additional treatment lines by the clinical cut-off date (supplemental table 5, available online). The most commonly used regimens included irinotecan and 5-FU/FA, with three patients (6%) receiving a further cetuximab-containing regimen and one (2%) bevacizumab. Forty-nine per cent of all patients had received all three active chemotherapy agents: 5-FU/FA, irinotecan and oxaliplatin.

PK evaluation

Cetuximab concentration data were available from 49 patients with trough and peak concentration values available from 29. For five patients who received 5-FU at 1500 mg/m² and 15 who received 5-FU at standard 2000 mg/m², a full PK profile following cetuximab administration in week 4 was available. PK

Table 2. Patient and disease characteristics at baseline

	Summary statistics		
	Part I, 5-FU 1500 mg/m ² (N = 8)	Part I and II, 5-FU standard 2000 mg/m ² (N = 41)	Total (N = 49)
Gender, N (%)			
Male	6 (75)	25 (61)	31 (63)
Female	2 (25)	16 (39)	18 (37)
Age, years			
Mean (SD)	59.3 (11.16)	62.0 (9.73)	61.5 (9.90)
Median (Q1–Q3)	63 (53–66)	62 (54–70)	62 (54–68)
Age characteristics, N (%)			
<65 years	6 (75)	24 (59)	30 (61)
≥65 years	2 (25)	17 (41)	19 (39)
ECOG performance status, N (%)			
0	7 (88)	28 (68)	35 (71)
1	1 (13)	11 (27)	12 (24)
2	0	2 (5)	2 (4)
Primary tumor location, N (%)			
Colon	3 (38)	29 (71)	32 (65)
Rectum	5 (63)	12 (29)	17 (35)
Number of sites involved, N (%)			
1	2 (25)	19 (46)	21 (43)
2	3 (38)	19 (46)	22 (45)
3	3 (38)	3 (7)	6 (12)
Sites involved, N (%)			
Liver	6 (75)	36 (88)	42 (86)
Lung	4 (50)	14 (34)	18 (37)
Nodes	5 (63)	13 (32)	18 (37)
Other	2 (25)	3 (7)	5 (10)

5-FU, 5-fluorouracil; SD, standard deviation; Q1–Q3, first to third interquartile range; ECOG, Eastern Cooperative Oncology Group.

data were similar across the two 5-FU dose levels indicating that the difference in doses had no effect on the PK of cetuximab. Mean cetuximab concentrations for week 4 are illustrated in supplemental figure 3, available online, and mean cetuximab serum/trough concentrations up to week 35 in supplemental figure 4, available online. In general, a similar level of intersubject variability in cetuximab concentration values was observed and trough concentrations appeared to be relatively stable throughout. All concentration values were in reasonable agreement with historical controls including previously examined cetuximab/irinotecan combinations [21, 22]. Mean PK parameters for week 4 are presented in supplemental table 6, available online. The best fit of the cetuximab data was obtained with a one-compartment model.

discussion

Several studies in previously untreated ACRC patients have now demonstrated an improved activity of the combination of

Table 3. Grade 3/4 treatment-related non-hematological adverse events according to preferred term occurring in three or more (>6%) subjects in the ITT/safety population

Adverse event	Number (%) of subjects, grade 3/4		
	Part I, 5-FU 1500 mg/m ² (N = 8)	Part I and II, 5-FU standard 2000 mg/m ² (N = 41)	Total (N = 49)
Any treatment related	6 (75)	26 (63)	32 (65)
Diarrhea	1 (13)	12 (29)	13 (27)
Vomiting	1 (13)	3 (7)	4 (8)
Paresthesia	1 (13)	7 (17)	8 (16)
Skin exfoliation	0	5 (12)	5 (10)
Nail disorder	0	5 (12)	5 (10)
Hypersensitivity	2 (25)	1 (2)	3 (6)
Folliculitis	2 (25)	1 (2)	3 (6)
Acne-like rash	0 (0)	1 (2)	1 (2)
Mucosal inflammation	0	3 (7)	3 (6)
Infusion-related reactions ^a	2 (25)	1 (2)	3 (6)

^aInfusion-related reaction is a composite category including the Medical Dictionary for Regulatory Activities 8.0 terms: Infusion-related reaction, Hypersensitivity, Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Dyspnea*, Pyrexia*, Chills* (*only taken into account when occurring on the first day of the first cetuximab administration). These composite category data are included to provide additional safety information of relevance to cetuximab administration.
5-FU, 5-fluorouracil.

cetuximab and chemotherapy [8, 13, 15]. Two recently reported large randomized trials showed an absolute increase in response rate of 8%–10% when cetuximab was combined with either oxaliplatin- or irinotecan-based chemotherapy as compared with first-line chemotherapy alone [14, 16]. The randomized phase III trial with irinotecan also met its primary objective in showing that the risk of progression was statistically significantly reduced in the cetuximab plus FOLFIRI compared with the FOLFIRI-alone arm (hazard ratio 0.851; *P* = 0.0479).

The present study has demonstrated that cetuximab in combination with FUFOX is a safe and well-tolerated regimen. The most common treatment-related grade 3/4 AEs in the standard 2000 mg/m² group were diarrhea (29% of patients) and paresthesia (17%, most likely related to oxaliplatin). Although grade 3/4 skin exfoliation and nail disorders were reported in 12% of patients in this group, the most common side-effect generally associated with the use of EGFR inhibitors, including cetuximab, is an acne-like rash, [18] reported at grade 3 for only one patient in the current study and neutropenia grade 3 in 4%. The ACROBAT study, investigating cetuximab combined with FOLFOX-4 in 43 previously untreated ACRC patients, reported similar grade 3/4 AEs, with diarrhea in 26% and paresthesia in 19% of patients, but higher rates of neutropenia (23%, likely to be caused by 5-FU bolus administration in the FOLFOX-4 regimen) and rash (16%) [15]. A second randomized phase II study (OPUS) reported grade 3/4 diarrhea, paresthesia and neutropenia at 7%, 1% and

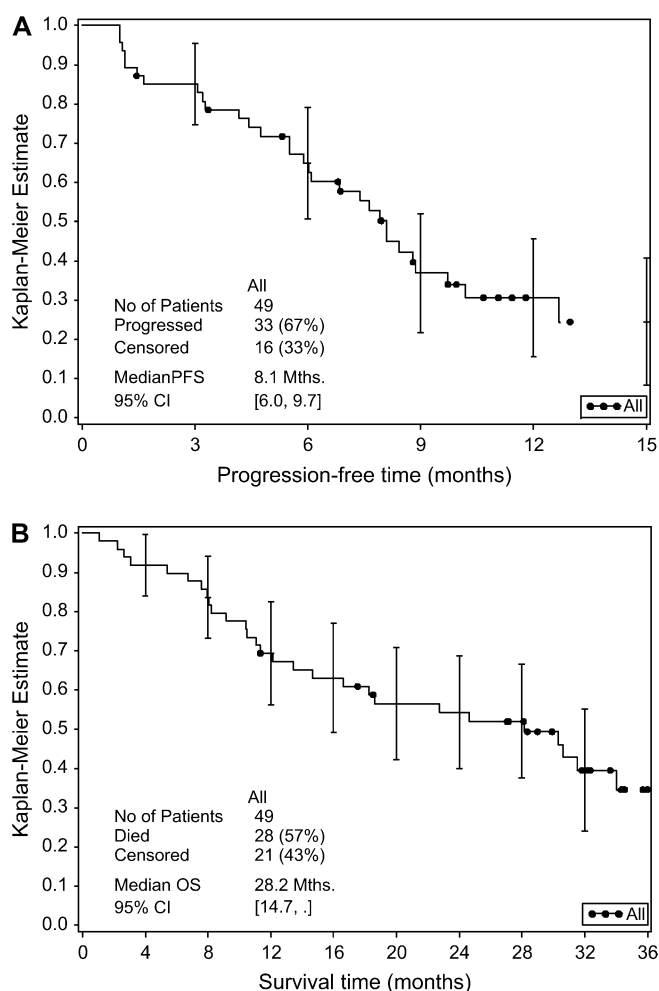
Table 4. Response rate and survival data

Efficacy variable	Number (%) of subjects: ITT/safety population		
	Part I, 5-FU 1500 mg/m ² , (N = 8)	Part I and II, 5-FU standard 2000 mg/m ² (N = 41)	Total (N = 49)
Best confirmed response			
CR	0	1 (2)	1 (2)
PR	5 (63)	22 (54)	27 (55)
SD	1 (13)	9 (22)	10 (20)
PD	1 (13)	6 (15)	7 (14)
NE	1 (13)	3 (7)	4 (8)
Confirmed response rate (%) (95% CI)	63 (25, 92)	56 (40, 72)	57 (42, 71)
Disease control rate (%) (95% CI)	75 (35, 97)	78 (62, 89)	78 (63, 88)
Median PFS, months ^a (95% CI)			8.1 (6.0, 9.7)
Median overall survival, ^a months (95% CI)			28.2 (14.7, n.a)

^aValues for PFS and overall survival were based on Kaplan–Meier estimates. ITT, intention to treat; 5-FU, 5-fluorouracil; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; response rate = CR + PR; disease control rate, CR + PR + SD; CI, confidence interval; PFS, progression-free survival.

28%, respectively, in the 170 ACRC patients in the cetuximab plus FOLFOX-4 arm [16]. Therefore, cetuximab with FUFOX seems to be less toxic compared to the combination with FOLFOX-4, with a low rate of acneiform rash and severe neutropenia.

The confirmed, investigator-assessed response rate of 56% was comparable to the 48% and 54% previously reported for the FUFOX combination [17, 23]. The median PFS figure of 8.1 months is also similar to that obtained for oxaliplatin/infusional 5-FU/FA combinations in previous studies, either with the FUFOX regimen (as reported in previous phase III trials: 7.9 and 8.0 months, respectively) [17, 23] or FOLFOX (8.1–9.0 months) [3, 24, 25]. However, the median OS time of 28.2 months for the cetuximab/FUFOX regimen was somewhat in contrast to the reported median OS times of only 16.2–20.6 months in the other 5-FU/FA/oxaliplatin trials [3, 23–25]. The apparent discrepancy in these survival times in the current study may be influenced by the favorable patient characteristics or may simply be a consequence of the small sample size (which confers only limited power to estimate the efficacy parameters of time-to-event variables). Furthermore, a relatively high percentage of patients received three or more treatment lines after progression, although the percentage of patients receiving all active chemotherapy agents was not higher in this study than in the trials with the highest OS reported. A median PFS of 12.3 months and a median OS of 30.0 months were reported for cetuximab/FOLFOX-4 in the ACROBAT trial, including a high resection rate of 23% [15] a factor that may have influenced the PFS. However, these challenging results could not be reproduced in the randomized phase 2 OPUS trial including 337 patients, where a response rate of 46% and a PFS of 7.2 months were observed [16]. The

**Figure 2.** Kaplan–Meier curves for progression-free (A) and overall survival (B).

favourable results of the ACROBAT trial [15] are merely due to selection of patients with favourable prognostic factors for a cetuximab-based combination chemotherapy. In addition to clinical factors (e.g. smaller metastases load), this could be related to molecular prognostic or predictive factors. However, therapeutic benefit from cetuximab appears to be independent of the level of tumor EGFR expression, as detected by immunohistochemistry [26–28]. In the search for a biological marker for either prognosis of mCRC or prediction of anti-EGFR treatment outcome, a number of uncontrolled single-agent studies with cetuximab have recently demonstrated that patients whose tumors show an objective response to cetuximab-based treatment almost invariably have a wild-type *KRAS* gene, with responses less common in the minority of patients whose tumors have activating *KRAS* mutations [29–33]. The possible role of *KRAS* mutation status as a predictor of clinical response to EGFR-targeted therapy was further emphasized by a retrospective analysis of a randomized phase III trial of panitumumab plus BSC versus BSC alone, which confirmed that the efficacy benefit of panitumumab monotherapy was confined essentially to CRC patients whose tumors lacked *KRAS* mutations at least in 3rd line treatment [34]. However, data on the influence of *KRAS* mutation on the

treatment outcome of EGFR-targeted therapy in combination with chemotherapy in earlier lines of treatment are at present very limited but promising [35].

In summary, the combination of cetuximab and FUFOX has demonstrated a relatively low toxicity profile. In particular, the absence of clinically relevant neutropenia and the low incidence of severe acneiform rash in comparison to FOLFOX-4 plus cetuximab make this protocol attractive as a basis for further combinations, e.g. triple chemotherapy combinations with cetuximab.

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Figure 3. [supplementary material]

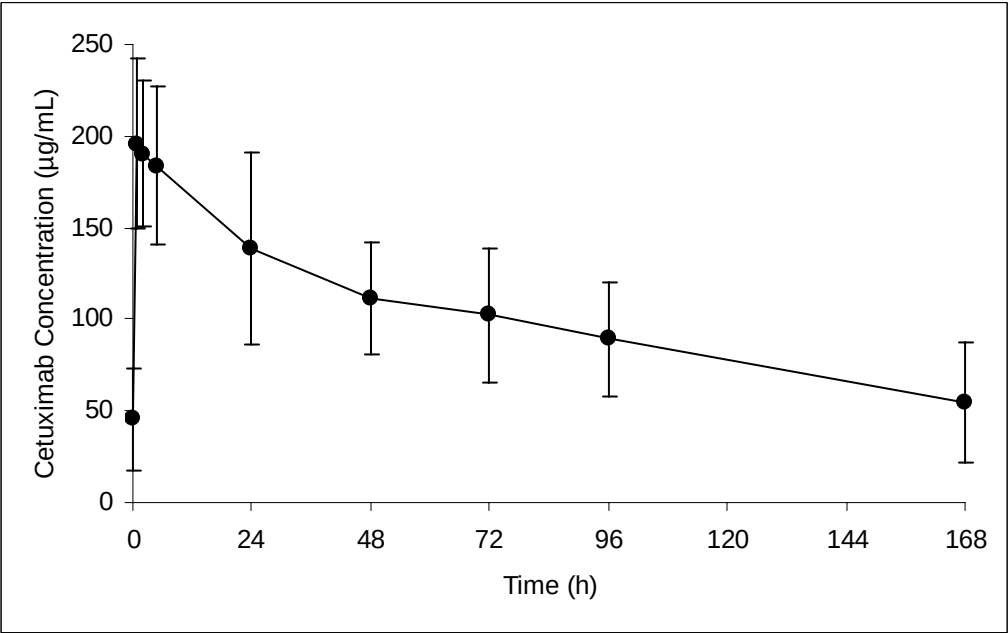


Figure 4. [supplementary material]

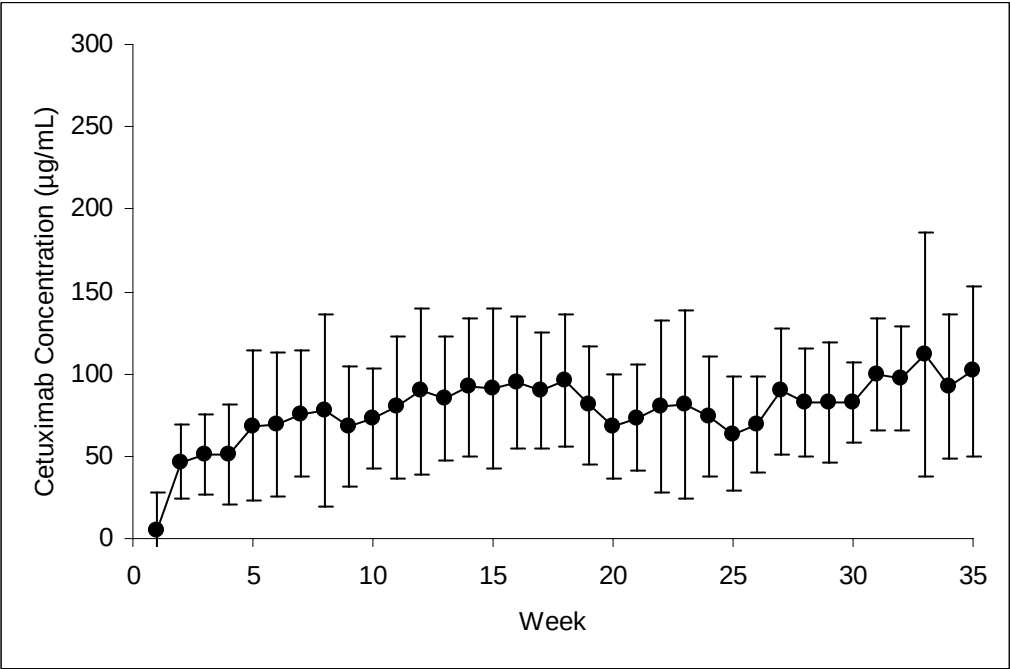


Table 5. Anti-cancer post-study treatment (ITT population) [supplementary material]

	Number of patients N=49 (%)
Patients with any salvage treatment	31 (63)
Salvage treatment: agents	
Irinotecan	24 (49)
5-FU	21 (43)
FA	21 (43)
Capecitabine	7 (14)
Other	7 (14)
Oxaliplatin	4 (8)
Cetuximab	3 (6)
Radiotherapy	2 (4)
Bevacizumab	1 (2)
Number of further treatment lines after end of study	
None	18 (37)
1	8 (16)
2	1 (2)
3	13 (27)
4	6 (12)
5	1 (2)
>5	2 (4)

5-FU, 5-fluorouracil; FA, folinic acid.

Table 6. Mean pharmacokinetic parameters in week 4 **[supplementary material]**

Parameter		Week 4 Cetuximab in combination with FUFOX (N=20)
C _{max} (µg/mL)	Mean (S.D.)	211 (44)
	Range	133 - 280
t _{max} (h)	Mean (S.D.)	3.8 (5)
	Range	1 - 24
AUC _τ (µg/mL*h)	Mean (S.D.)	16388 (5575)
	Range	7306 - 30547
λ _z (1/h)	Mean (S.D.)	0.008 (0.004)
	Range	0.002 - 0.02
t _{1/2} (h)	Mean (S.D.)	108.4 (54.8)
	Range	33.9 - 277.4
MRT _{ss} (h)	Mean (S.D.)	157 (86)
	Range	50 - 433
CL _{ss} (L/h)	Mean (S.D.)	0.032 (0.013)
	Range	0.016 - 0.068
V _{ss} (L)	Mean (S.D.)	4.46 (2)
	Range	2.15 - 11.43
C _{pre} (µg/mL)	Mean (S.D.)	44.7 (29.1)
	Range	0 - 107
C _{min} (µg/mL)	Mean (S.D.)	44.4 (27.7)
	Range	1 - 107
C _{av} (µg/mL)	Mean (S.D.)	97.6 (33.2)
	Range	43.5 - 181.8
PTF (%)	Mean (S.D.)	187 (66)
	Range	86 - 375

S.D., standard deviation

