original article

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Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamic phase I dose-escalation study

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Background: This phase I dose-escalation study was designed to determine the maximum tolerated dose (MTD) and recommended dose of cetuximab administered on an every-second-week schedule to patients with metastatic colorectal cancer, on the basis of safety, pharmacokinetic and pharmacodynamic evaluation.
Patients and methods: The study comprised two parts: a 6-week cetuximab monotherapy dose-escalation phase and a subsequent combination therapy phase, during which patients received cetuximab, at the same dose/schedule as in the monotherapy phase, followed by irinotecan plus infusional 5-fluorouracil/folinic acid (FOLFIRI). Patients in the control group received cetuximab as a 400 mg/m^2 initial dose, then 250 mg/m^2/week and in the dose-escalation group, at 400–700 mg/m^2, every second week.
Results: Sixty-two patients were included in the study. The MTD of cetuximab administered on an every-second-week schedule was not reached. The safety profiles were similar across all groups. Response rates in the cetuximab monotherapy and combination therapy phases were 15% and 42%, respectively. Trough levels for the 500, 600 mg/m^2 and standard weekly regimens were comparable.
Conclusion: Cetuximab can be safely administered once every second week at doses between 400 and 700 mg/m^2, with 500 mg/m^2 being the most convenient and feasible dose for future studies.
Key words: cetuximab, EGFR, every second week, metastatic colorectal cancer, pharmacokinetics

introduction

The addition of biological agents to conventional chemotherapy regimens for the treatment of metastatic colorectal cancer (mCRC) is an effective way to improve the efficacy of such treatments [1]. One agent that has been shown to be particularly efficacious in this setting is the epidermal growth factor receptor (EGFR)-targeting immunoglobulin (Ig)G1 mAb cetuximab [Erbitux® developed by Merck (Darmstadt, Germany), under licence from Imclone]. Binding of cetuximab to EGFR, which is expressed by the majority of colorectal tumours [2–6], competitively inhibits ligand binding and downstream signalling [7], stimulates receptor internalisation and degradation [8, 9] and may trigger an antitumour antibody-dependent cell-mediated cytotoxicity reaction [10, 11]. The maximum tolerated dose (MTD) of cetuximab was not reached in early dose-finding studies. The recommended dose (RD) was consequently on the basis of pharmacokinetic (PK) and safety data. Cetuximab clearance, equating to full receptor occupancy, was shown to be saturated at weekly doses >200 mg/m^2 [12]. On the basis of these data, the standard weekly regimen comprising an initial 2-h infusion of 400 mg/m^2 followed by weekly 1-h infusions of 250 mg/m^2 was adopted for phase II and III studies.

The efficacy of cetuximab administered weekly in the first- and subsequent-line treatment of mCRC has been demonstrated in a series of randomised studies [3, 13–16]. However, the most commonly used chemotherapy regimens for the treatment of mCRC, infusional 5-fluorouracil (5-FU) combined with either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX), are administered on an every-second-week basis.

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Table 1. Patient and disease characteristics at baseline

Variable	Cetuximab weekly	Cetuximab every second week				All patients
	400/250 mg/m^2 (n = 13)	400 mg/m^2 (n = 13)	500 mg/m^2 (n = 14)	600 mg/m^2 (n = 12)	700 mg/m^2 (n = 10)	(n = 62)
Age (years)						
Median	67.0	66.0	68.5	59.0	63.5	65.0
Range	55–75	47–77	42–80	41–78	39–73	39–80
Gender, n (%)						
Male	6 (46)	9 (69)	11 (79)	9 (75)	4 (40)	39 (63)
Female	7 (54)	4 (31)	3 (21)	3 (25)	6 (60)	23 (37)
ECOG PS, n (%)						
0	7 (54)	11 (85)	13 (93)	10 (83)	8 (80)	49 (79)
1	5 (39)	2 (15)	1 (7)	2 (17)	0 (–)	10 (16)
2	1 (8)	0 (–)	0 (–)	0 (–)	2 (20)	3 (5)
Site of primary, n (%)						
Colon	8 (62)	9 (69)	5 (36)	7 (58)	7 (70)	36 (58)
Rectum	5 (38)	4 (31)	8 (57)	3 (25)	3 (30)	23 (37)
Colon/rectum	0 (–)	0 (–)	1 (7)	2 (17)	0 (–)	3 (5)
Prior chemotherapy, n (%)						
Neo/adjuvant	3 (23)	2 (15)	4 (29)	1 (8)	1 (10)	11 (18)
None	10 (77)	11 (85)	10 (71)	11 (92)	9 (90)	51 (82)

ECOG PS, Eastern Cooperative Oncology Group performance status.

The synchronisation of cetuximab administration with that of the chemotherapy would simplify treatment schedules for the patient and, by potentially halving the number of hospital visits, would most likely reduce the overall cost of treatment for the health care provider. The prolonged half-life of cetuximab has prompted the evaluation of administration on an every-second-week basis. The initial monotherapy phase of this two-part phase I study was therefore designed to establish the RD for cetuximab administered every second week. Subsequently, the combination therapy phase aimed to evaluate cetuximab at the tested doses in combination with FOLFIRI in relation to safety and efficacy. Patients in the control arm received the standard weekly cetuximab regimen, as monotherapy and then in combination with FOLFIRI. An important part of exploring whether the every-second-week administration of cetuximab was feasible was to demonstrate that the PK and pharmacodynamic parameters for this and the standard weekly regimen were comparable and further that there were no marked differences in the safety or efficacy profiles of cetuximab administered at the every-second-week RD compared with the standard weekly dose.

patients and methods

patient eligibility

Patients were eligible for inclusion if they were at least 18 years of age with histologically confirmed EGFR-expressing mCRC. EGFR expression was evaluated using a DakoCytomation pharmDx™ immunohistochemistry kit (Dako, Glostrup, Denmark), with one tumour cell staining to any intensity being the minimum criterion required to confirm expression. Patients were required to have at least one tumour site accessible for biopsy and at least one bi-dimensionally measurable lesion, not in an irradiated area. They also had to have an Eastern Cooperative Oncology Group performance status of two or less, a life expectancy of ≥12 weeks and adequate bone marrow, liver, and renal function. Principal exclusion criteria were previous exposure to EGFR-targeting therapy, previous chemotherapy for mCRC, previous adjuvant treatment within 6 months of study entry, surgery or irradiation within 30 days of study entry, or known or suspected brain metastases.

The protocol was reviewed by independent ethics committees at each centre and the study was carried out according to the principles of the Declaration of Helsinki. All patients provided informed consent.

study design and dosing

This multicentre phase I study was divided into two parts: a monotherapy phase lasting 6 weeks and a combination therapy phase, during which patients received cetuximab, at the same dose/schedule as during the monotherapy phase, followed after 1 h (every second week in the control arm) by irinotecan, infused over 30–90 min, at 180 mg/m^2; folinic acid, infused over 2 h at 400 mg/m^2 (*rac*; 200 mg/m^2 if L form); and then 5-FU given as a bolus injection at 400 mg/m^2 followed by a continuous infusion of 2400 mg/m^2 over 46 h (FOLFIRI). Treatment was continued until the occurrence of progressive disease (PD) or unacceptable toxicity. Patients with unacceptable chemotherapy-related toxicity could continue on cetuximab monotherapy.

The primary objective was to determine the MTD (equivalent to the RD) of cetuximab when administered to patients with mCRC every second week for 6 weeks, on the basis of the occurrence of dose-limiting toxicity (DLT). Secondary objectives included assessments of safety, PK, best overall response (each phase), progression-free survival (PFS), and [as extensively reported [17]] pharmacodynamic, pharmacogenomic and pharmacoproteomic end points. PK and pharmacodynamic results were to be taken into consideration when determining the RD of cetuximab administered every second week.

Patients were assigned sequentially to either the standard-dose group or the dose-escalation group. All patients received antihistamine premedication for the cetuximab infusions. The standard-dose group received an initial 2-h infusion of cetuximab 400 mg/m^2, followed by weekly doses of 250 mg/m^2, infused over 1 h. The first cohort of nine fully assessable patients in the dose-escalation group were to receive an initial cetuximab infusion of 400 mg/m^2 followed by infusions of 400 mg/m^2 every

Table 2. Exposure to treatment

Variable	Cetuximab weekly	Cetuximab every second week			
	400/250 mg/m^2 (n = 13)	400 mg/m^2 (n = 13)	500 mg/m^2 (n = 14)	600 mg/m^2 (n = 12)	700 mg/m^2 (n = 10)[a]
Cetuximab monotherapy					
Cumulative dose, mg/m^2					
Median	1650	1200	1497	1793	2093
Q1–Q3	1634–1690	1196–1209	1483–1507	1781–1803	2040–2104
Dose intensity, mg/m^2/week					
Median	275	201	250	298	346
Q1–Q3	272–283	199–205	247–252	294–308	342–350
Relative dose intensity, n (%)					
80% to <90%	0 (–)	1 (8)	0 (–)	0 (–)	1 (10)
≥90%	13 (100)	12 (92)	14 (100)	12 (100)	9 (90)
Combination therapy					
Cetuximab					
Median duration of treatment, weeks[b]	28.1	36.0	42.1	27.9	31.5
Cumulative dose, mg/m^2					
Median	4609	5916	7893	5356	8200
Q1–Q3	2881–7981	3836–7371	6869–14 222	4160–8425	5804–11 188
Dose intensity (mg/m^2/week)					
Median	238	193	230	286	293
Q1–Q3	223–246	184–198	219–237	278–292	288–334
Relative dose intensity, n (%)					
60% to <80%	2 (15)	0 (–)	2 (14)	0 (–)	0 (–)
80% to <90%	2 (15)	2 (15)	4 (29)	1 (8)	5 (56)
≥90%	9 (69)	11 (85)	8 (57)	11 (92)	4 (44)
Irinotecan					
Median duration of treatment, weeks	19.7	30.0	36.1	20.5	28.0
Relative dose intensity, n (%)					
<60%	1 (8)	0 (–)	1 (7)	0 (–)	1 (11)
60% to <80%	4 (31)	3 (23)	5 (36)	1 (8)	2 (22)
80% to <90%	2 (15)	2 (15)	4 (29)	2 (17)	0 (–)
≥90%	6 (46)	8 (62)	4 (29)	9 (75)	6 (67)
5-FU					
Median duration of treatment, weeks	19.9	30.1	36.2	20.6	28.1
Relative dose intensity, n (%)					
<60%	2 (15)	0 (–)	1 (7)	0 (–)	1 (11)
60% to <80%	3 (23)	4 (31)	4 (29)	1 (8)	2 (22)
80% to <90%	2 (15)	1 (8)	6 (43)	2 (17)	1 (11)
≥90%	6 (46)	8 (62)	3 (21)	9 (75)	5 (56)

[a]n = 9 for combination therapy phase.
[b]Total for monotherapy plus combination therapy phases.
Q1–Q3, first to third inter-quartile range; 5-FU, 5-fluorouracil.

second week (2-h infusions of 200 ml/m^2 of solution). If no or one of the patients treated at this starting dose level experienced DLT, successive cohorts of nine fully assessable patients were to be entered at each of the subsequent dose levels (of 500, 600 and 700 mg/m^2, in volumes of 250, 300 and 350 ml/m^2, infused over 2.5, 3 or 3.5 h, respectively). If DLT occurred in two or more patients treated at the same dose level, escalation was terminated; if two patients showed DLTs, the MTD had been reached at that dose level; alternatively, if three or more patients experienced DLTs, the dose level below was considered to be the MTD. Intrapatient dose escalation was not permitted. DLT was defined as any grade 3 or 4 haematological or non-haematological toxicity [except for infusion-related reactions (IRRs) and grade 3 skin toxicity occurring during the first 6 weeks of treatment] or administration of <66% of the assigned dose (i.e. a delay of >14 days in the first 6 weeks) due to toxicity at any of the cetuximab doses.

statistical methods and considerations

The primary target variable was the MTD of cetuximab monotherapy measured by DLT observed during the first 6 weeks of treatment. Efficacy and safety assessments were carried out on the intention to treat (ITT)/safety population. Response was assessed by the investigators according to modified criteria of the World Health Organization. Imaging of the chest,

Table 3. Treatment-related grade 3/4 adverse events

MedDRA-preferred term, *n* (%)	Cetuximab weekly	Cetuximab every second week				All patients ($n = 61$)[b]
	400/250 mg/m^2 ($n = 13$)	400 mg/m^2 ($n = 13$)	500 mg/m^2 ($n = 14$)	600 mg/m^2 ($n = 12$)	700 mg/m^2 ($n = 9$)[a]	
Monotherapy						
Rash	–	1 (8)	–	–	–	1 (2)
Combination therapy						
Any	11 (85)	7 (54)	11 (79)	5 (42)	7 (78)	41 (67)
Diarrhoea	5 (38)	6 (46)	4 (29)	2 (17)	1 (11)	18 (30)
Neutropenia	6 (46)	1 (8)	4 (29)	3 (25)	1 (11)	15 (25)
Rash	–	–	5 (36)	1 (8)	3 (33)	9 (15)
Conjunctivitis	1 (8)	–	1 (7)	–	1 (11)	3 (5)
Febrile neutropenia	1 (8)	–	2 (14)	–	–	3 (5)
Vomiting	1 (8)	1 (8)	1 (7)	–	–	3 (5)
Asthenia	–	1 (8)	1 (7)	–	–	2 (3)
Mucosal inflammation	1 (8)	–	–	–	1 (11)	2 (3)
Deep vein thrombosis	1 (8)	–	1 (7)		–	2 (3)
Abdominal pain	–	–	–	–	1 (11)	1 (2)
Hypocalcaemia	–	–	1 (7)	–	–	1 (2)
Hyperglycaemia	–	1 (8)	–	–	–	1 (2)
Hypomagnesaemia	–	–	1 (7)	–	–	1 (2)
Myocardial ischaemia	–	1 (8)	–	–	–	1 (2)
Nail disorder	–	–	–	–	1 (11)	1 (2)
Nausea	1 (8)	–	–	–	–	1 (2)
Paronychia	–	–	–	–	1 (11)	1 (2)
Skin infection	–	–	1 (7)	–	–	1 (2)
Skin fissures	–	–	1 (7)	–	–	1 (2)
Pulmonary embolism	–	–	1 (7)	–	–	1 (2)
Acne-like rash[c]						
Monotherapy	–	1 (8)	–	–	–	1 (2)
Combination therapy	–	–	5 (36)	1 (8)	3 (33)	9 (15)

MedDRA, Medical Dictionary for Regulatory Activities.
[a]$n = 10$ for monotherapy phase.
[b]$n = 62$ for monotherapy phase.
[c]Acne-like rash is a special adverse event category, comprising MedDRA 8.1 terms: acne, acne pustular, dermatitis acneiform, dry skin, erythema, folliculitis, pruritus, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin hyperpigmentation, telangiectasia, xerosis.

abdomen and pelvis was carried out at baseline by computed tomography or magnetic resonance imaging. Subsequently, lesions were assessed every 6 weeks to monitor disease progression. Treatment-emergent adverse events (AEs) occurring from the first day of study medication until 6 weeks after the last dose were graded using the National Cancer Institute—Common Toxicity Criteria, Version 2.

PFS time was defined as the duration from the first infusion of cetuximab until the first observation of radiologically confirmed disease progression or death due to any cause when this occurred within 60 days of the last tumour response assessment or of the day of the first cetuximab infusion (whichever was later). The Kaplan–Meier method [18] was used to investigate PFS time.

PK analysis

For the PK analysis of cetuximab, 2.5-ml blood samples were taken in the standard-dose group on day 1 [before and at the end of infusion (EOI)], on days 8, 15 and 22 before EOI, and on day 29 before and at the EOI, and 4, 24, 48, 96 and 168 h after the start of infusion. In the dose-escalation group, blood samples were taken on day 1 before and at the EOI, on day 15 before EOI and on day 29 before and at the EOI, and 4, 24, 48, 96, 168, 240, 288 and 336 h after the start of infusion. Starting with day 43 in both dose groups, blood samples for PK analysis were collected before each cetuximab infusion until the occurrence of PD. Serum was extracted from blood immediately and stored at −20°C until analysis.

Analysis of serum samples was carried out using a validated sandwich enzyme-linked immunosorbent assay. The lower and upper limits of quantification for the undiluted cetuximab samples were 0.25 and 7.5 μg/ml, respectively. Calculation of PK parameters was carried out from concentration data derived after cetuximab infusion on day 29 according to noncompartmental methods using the PK software programme KINETICA, version 4.1.1 (InnaPhase Corp., Philadelphia, PA). PK analysis included determinations of maximum serum concentration (C_{max}), trough plasma concentration (C_{min}), time to maximum concentration (t_{max}), average serum concentration at steady state (C_{av}), area under the plasma concentration–time curve from time zero to the last sampling time (AUC_{0-t}), apparent terminal elimination half-life associated with the negative terminal slope ($t_{1/2}$), total body clearance of drug from plasma (CL), trough concentrations before the second infusion and the volume of distribution at steady state (V_{ss}).

pharmacodynamic studies

Skin biopsies were taken at baseline and week 4 for immunohistochemical expression analyses of a panel of markers associated with EGFR signalling.

Table 4. Efficacy

Efficacy variable	Cetuximab weekly	Cetuximab every second week				All patients
	250 mg/m^2 (n = 13)	400 mg/m^2 (n = 13)	500 mg/m^2 (n = 14)	600 mg/m^2 (n = 12)	700 mg/m^2 (n = 10)	(n = 62)
Monotherapy						
Response, n (%)						
Complete response	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Partial response	1 (8)	1 (8)	3 (21)	3 (25)	1 (10)	9 (15)
Stable disease	6 (46)	7 (54)	7 (50)	5 (42)	7 (70)	32 (52)
Progressive disease	6 (46)	5 (38)	4 (29)	4 (33)	1 (10)	20 (32)
Not evaluable	0 (–)	0 (–)	0 (–)	0 (–)	1 (10)	1 (2)
Overall response rate, % (95% CI)	8 (0.2–36)	8 (0.2–36)	21 (5–51)	25 (6–57)	10 (0.3–45)	15 (7–26)
Disease control rate, % (95% CI)	54 (25–81)	62 (32–86)	71 (42–92)	67 (35–90)	80 (44–98)	66 (53–78)
Combination therapy						
Response, n (%)						
Complete response	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Partial response	4 (31)	5 (38)	8 (57)	4 (33)	5 (50)	26 (42)
Stable disease	7 (54)	7 (54)	6 (43)	6 (50)	3 (30)	29 (47)
Progressive disease	2 (15)	0 (–)	0 (–)	1 (8)	1 (10)	4 (6)
Not evaluable	0 (–)	1 (8)	0 (–)	1 (8)	1 (10)	3 (5)
Overall response rate, % (95% CI)	31 (9–61)	38 (14–68)	57 (29–82)	33 (10–65)	50 (19–81)	42 (30–55)
Disease control rate, % (95% CI)	85 (55–98)	92 (64–100)	100 (77–100)	83 (52–98)	80 (44–98)	89 (78–95)
PFS time, months						
Median (95% CI)	4.4 (3.2–9.5)	9.4 (4.6–12.2)	13.6 (9.2–17.4)	6.9 (4.3 to NR)	6.3 (2.7–8.4)	8.4 (6.3–9.5)
PFS rate, %						
6 months (95% CI)	38 (12–65)	60 (32–87)	90 (71–100)	67 (36–99)	60 (30–90)	63 (50–76)
12 months (95% CI)	—	26 (0–54)	60 (24–96)	—	18 (0–48)	25 (10–39)

CI, confidence interval; PFS, progression-free survival; NR, not reached.

In order to screen for biomarkers associated with response to cetuximab, tumour and plasma biopsies were also taken at baseline and week 4 and used, respectively, in gene expression microarray and proteomic evaluations. Mutation analysis was carried out on archival formalin-fixed paraffin-embedded tumour tissue to assess the impact of somatic *KRAS* mutations on the clinical activity of cetuximab. Processing of the samples, analytical methods and associated statistical analyses are described in full in a separate manuscript [17].

results

patient and baseline characteristics

From September 2004 to August 2006, 62 Caucasian patients were enrolled at four centres in two European countries and entered into the monotherapy phase of the study; all received at least one infusion of cetuximab (ITT/safety population). Sixty-one patients entered the combination therapy phase of the study and received at least one infusion of cetuximab and FOLFIRI. Complete PK analyses were conducted on 46 patients. Baseline patient and disease characteristics were generally well balanced between the treatment groups (Table 1).

exposure to study treatment

Exposure to study treatment is summarised in Table 2. In the monotherapy phase, 97% of patients achieved a relative dose intensity (RDI) for cetuximab of ≥90%. In the combination therapy phase, 70% of patients achieved an RDI for cetuximab of ≥90% with 93% achieving an RDI ≥80%. The longest median durations of cetuximab treatment were seen in the 400 and 500 mg/m^2 groups (36.0 and 42.1 weeks, respectively). These figures compare favourably with 28.1 weeks for patients receiving the standard weekly regimen (Table 2). The RDIs for irinotecan and 5-FU were between 80% and 100% for 70% of patients in each case.

Cetuximab treatment was delayed during the monotherapy phase in six (10%) patients due to AEs (intestinal perforation and hepatic haematoma, one patient each at 250 mg/m^2; rash, one patient at 400 mg/m^2; abdominal pain and constipation, one patient at 600 mg/m^2; and *Escherichia* bacteraemia and tonsillitis, one patient each at 700 mg/m^2). Cetuximab treatment was delayed due to AEs in the combination therapy phase in 36 patients (59%; 62% and 58% of patients, respectively, receiving cetuximab weekly and every second week). The most frequent reasons were diarrhoea (10 patients, 16%), rash, and neutropenia (both 9 patients, 15%). The cetuximab dose was not reduced due to AEs in the monotherapy phase and was reduced in the combination therapy phase in only one patient in the 500 mg/m^2 dose group, because of skin fissures.

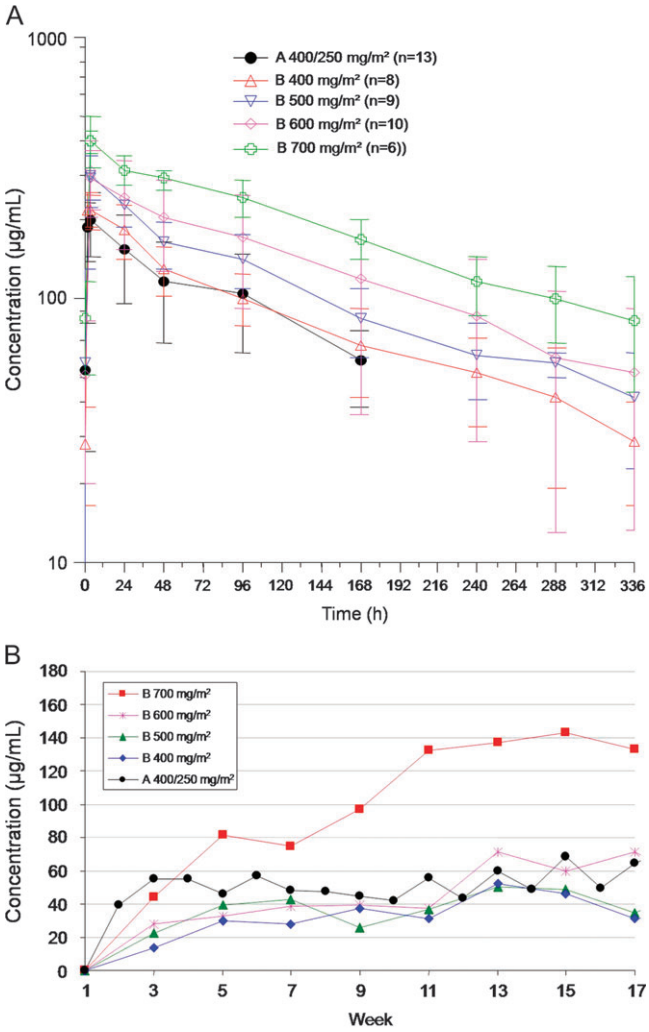

Figure 1. Pharmacokinetic evaluations. (A) Mean (±standard deviation) serum cetuximab concentrations at week 5 (logarithmic scale); (B) Median serum cetuximab trough concentrations (μg/ml).

dose-limiting toxicity

DLT was not reported for any of the patients receiving 400, 500 or 600 mg/m^2 of cetuximab every second week. Following dose escalation, a DLT (grade 4 dyspnoea) developed in one of 10 patients treated at 700 mg/m^2. The MTD was therefore not reached.

adverse events

The most common cetuximab-related AEs in the monotherapy phase were skin and s.c. tissue disorders (97% of patients, predominantly rash). With the exception of one case of rash (grade 3), all events were grade 1 or 2. In the combination therapy phase, the most common treatment-related AEs were gastrointestinal disorders (90% of patients; mainly diarrhoea) followed by skin and s.c. tissue disorders (80% of patients; mainly rash). As summarised in Table 3, the most frequently reported treatment-related grade 3/4 AEs observed during the combination therapy phase were diarrhoea (30%), neutropenia (25%), and rash (15%).

No patients experienced grade 3/4 IRRs. Thirteen patients (21%) developed a grade 1/2 IRR during cetuximab monotherapy, and two further patients developed a grade 1 IRR during combination therapy. Acne-like skin rash was reported for 60 patients (97%) in the monotherapy phase, reaching grade 3 in only one patient (2%) at 400 mg/m^2. In the combination therapy phase, acne-like rash reached grade 3 in nine (15%) patients (Table 3).

The patient who experienced grade 4 dyspnoea during the monotherapy phase died 14 days after the first dose of 700 mg/m^2 of cetuximab due to disease progression. Twelve further patients died within 30 days after the last dose of study treatment, due to disease progression (four patients), unrelated illness (four patients), disease-related complication (two patients) or unknown cause (two patients). None of the deaths were considered to be related to study treatment.

activity

Overall, in the monotherapy phase of the study, 9 (15%) patients had a partial response (PR), 32 (52%) showed stable disease (less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions), and 20 (32%) had PD (Table 4). Hence, the best overall response rate was 15% and the overall disease control rate 66%. Analysable DNA was extracted from the archival tumour tissue of 48 patients in the ITT/safety population. *KRAS* codon 12 or 13 mutations were detected in 19 of 48 tumours (40%). Responses to cetuximab monotherapy were seen in 8 of 29 patients whose tumours were wild type for *KRAS* and zero of 19 patients whose tumours carried *KRAS* mutations ($P = 0.015$).

In the cetuximab plus FOLFIRI combination therapy phase of the study, 26 (42%) patients showed a PR, 29 (47%) stable disease, and 4 (6%) PD, the best overall response rate therefore being 42% and the overall disease control rate 89%. There were no notable differences in response rate between the dose groups. The overall median PFS time was 8.4 months. The risk of disease progression was lower in patients whose tumours were *KRAS* wild type compared with those whose tumours carried *KRAS* mutations (median PFS time 9.4 versus 5.6 months, respectively, hazard ratio 0.47, log-rank $P = 0.0475$).

pharmacokinetics

Across all treatment groups, a similar level of interpatient variability was observed in the cetuximab concentration–time profiles of week 5 (Figure 1A). Trough concentration values for the 500 and 600 mg/m^2 every-second-week dosing regimen were comparable to the current standard weekly regimen. Cetuximab serum trough concentrations for the 700 mg/m^2 every-second-week regimen deviated substantially from the other dose regimens, with higher trough concentrations in conjunction with delayed steady-state conditions. The 700 mg/m^2 dose group did not reach steady state on week 5 when PK evaluations were carried out. When steady state seemed to be reached (around week 11), the median trough concentration was roughly twice that of the other doses (Figure 1B). Cetuximab serum concentrations and exposure increased with dose. The increase in AUC_{0-t} and C_{av} for the

Table 5. Pharmacokinetic parameters of cetuximab at steady state (individual serum concentration data derived during week 5)

Variable	Cetuximab weekly	Cetuximab every second week			
	400/250 mg/m^2 (n = 13)	400 mg/m^2 (n = 8)	500 mg/m^2 (n = 9)	600 mg/m^2 (n = 10)	700 mg/m^2 (n = 6)
C_{max}, μg/ml					
Mean (SD)	210 (54)	237 (32)	306 (63)	309 (93)	447 (63)
Range	140–293	179–277	215–421	171–528	395–541
t_{max} (h)					
Median	3.75	3.00	4.00	4.00	3.63
Range	1.0–5.25	2.0–24.0	1.0–24.0	3.0–20.25	3.25–4.22
AUC_{0-t} (μg/ml*h)					
Mean (SD)	17 787 (6739)	28 202 (6711)	35 794 (8180)	44 392 (22 349)	60 927 (9340)
Range	9984–29 719	20 416–39 118	23 840–46 775	21 272–97 508	50 548–72 336
C_{av} (μg/ml)					
Mean (SD)	105.9 (40.1)	83.9 (20.0)	106.5 (24.3)	132.1 (66.5)	181.3 (27.8)
Range	59.4–176.9	60.8–116.4	71.0–139.2	63.3–290.2	150.4–215.3
$t_{1/2}$ (h)					
Mean (SD)	100.6 (32.3)	134.7 (38.6)	137.0 (44.5)	133.2 (20.4)	156.1 (48.5)
Range	41.4–159.1	65.8–178.7	71.4–207.8	100.7–163.4	110.3–236.5
CL (l/h)					
Mean (SD)	0.027 (0.009)	0.027 (0.007)	0.026 (0.008)	0.028 (0.011)	0.019 (0.004)
Range	0.015–0.044	0.019–0.039	0.018–0.041	0.010–0.052	0.015–0.027
V_{ss} (l)					
Mean (SD)	3.82 (1.38)	4.90 (1.09)	4.76 (1.40)	5.32 (1.76)	4.11 (0.93)
Range	1.92–6.64	3.57–6.70	3.56–8.03	2.34–9.18	2.98–5.58
C_{min} (μg/ml)					
Mean (SD)	49.6 (26.1)	25.6 (11.8)	34.7 (16.0)	47.3 (30.8)	69.9 (25.4)
Range	11.0–82.9	6.4–42.0	7.2–52.7	20.4–113.0	46.7–110.0

C_{max}, maximal plasma concentration; SD, standard deviation; t_{max}, time to maximum concentration; AUC_{0-t}, area under the plasma concentration–time curve from zero to infinity; C_{av}, mean plasma concentration; $t_{1/2}$, terminal half-life; CL, total plasma clearance; V_{ss}, volume of distribution at steady state; C_{min}, trough plasma concentration.

every-second-week 400, 500, 600 and 700 mg/m^2 dosing regimens was approximately dose proportional. PK parameters $t_{1/2}$, CL and V_{ss} were comparable between the standard weekly and every-second-week 400, 500 and 600 mg/m^2 dosing regimens. In terms of exposure, the every-second-week 500 mg/m^2 dosing regimen matched more similarly the exposure of the 250 mg/m^2 weekly schedule (AUC_{0-t} 35 794 versus 35 574 μg/ml*h). Derived PK parameters at week 5 (Table 5) indicated differences in PK for the 700 mg/m^2 every-second-week regimen compared with the other dose regimens (prolonged half-life, reduced clearance).

immunohistochemical analysis of the EGFR-signalling pathway

As measured by immunohistochemistry in paired skin biopsies, the levels of EGFR signalling inhibition at week 4 (trough concentrations) were comparable in the weekly and the every-second-week schedules, with no relevant differences apparent across the dose-level groups (data not shown).

discussion

This study has demonstrated that cetuximab can be safely administered as monotherapy and in combination with FOLFIRI at doses between 400 and 700 mg/m^2 on a once every-second-week schedule. Grade 3 acne-like rash was observed in 16% of patients. This incidence rate is comparable to that reported in previous studies employing a standard weekly administration schedule [3, 16, 19]. Similarly, as grade 3/4 IRRs were not reported, every-second-week administration did not appear to have increased the frequency or intensity of such reactions. At 30% overall, the incidence of grade 3/4 diarrhoea was higher than has been previously reported for standard weekly cetuximab combined with FOLFIRI [16, 19]. However, there was no indication in the current study that this higher incidence was associated with every second week compared with standard weekly administration of cetuximab (Table 3) and may therefore have been a consequence of the particular two-part study design.

On the basis of the results of this study, other authors have confirmed the feasibility of cetuximab administration at 500 mg/m^2 every second week. Pfeiffer et al. [20] reported that salvage therapy with an every-second-week 500 mg/m^2 cetuximab plus irinotecan regimen was convenient, effective and well tolerated in patients with advanced colorectal cancer (CRC) in whom prior 5-FU, irinotecan and oxaliplatin had failed. Furthermore, in a study of advanced CRC patients who had progressed after at least one line of prior therapy, Martin-Martorell et al. [21] concluded that the efficacy and toxicity of cetuximab plus irinotecan were very similar when cetuximab was administered on a weekly and a once every-second-week schedule. It was apparent from these studies that the

every-second-week administration of cetuximab was not associated with an increase in the risk of IRRs or other cetuximab-associated side-effects, such as acne-like rash. Furthermore, data from the EVEREST dose-escalation study indicated that weekly administration of cetuximab at 500 mg/m^2 was generally well tolerated in patients who had no or only mild skin reactions after an initial 3 weeks of standard cetuximab therapy [22].

In the present study, cetuximab administered weekly or every second week was generally well tolerated. The median durations of cetuximab treatment in the every-second-week schedule compared favourably with that of patients receiving the standard weekly regimen. The low numbers of patients in each group preclude the drawing of firm conclusions regarding the relative activity of the different regimens. In the monotherapy phase of the study, nine of 62 patients responded to treatment, giving an overall response rate of 15%. Considering in particular the 48 patients analysed for *KRAS* tumour mutation status, responses were only apparent in the subgroup whose tumours were wild type for *KRAS* (8 of 29 patients, 28%), with no responses reported for those (0 of 19) whose tumours were carrying mutations of the gene ($P = 0.015$). Overall, the risk of disease progression was also found to be significantly lower in patients with *KRAS* wild type compared with *KRAS*-mutant tumours (hazard ratio 0.47; $P = 0.0475$), further highlighting the importance of *KRAS* status as clinical biomarker (these analyses are reported in full elsewhere). Although a degree of caution should be exercised given the small number of patients enrolled in this phase I study, the efficacy data are nevertheless consistent with the retrospective *KRAS* mutation analyses of the randomised CRYSTAL [16] and OPUS [13] studies, in that they confirm that the benefit of cetuximab treatment in the first-line setting is limited to patients with *KRAS* wild-type tumours. In the combination therapy phase, the overall response rate was 42%. This is comparable with first-line response rates for cetuximab plus FOLFIRI of 47% reported for other studies [16, 19].

PK parameters of cetuximab following the weekly standard dosing regimen were in good agreement with published data [23]. Trough concentration values for the 500 and 600 mg/m^2 every-second-week dosing regimen were comparable to the current standard weekly regimen, in contrast to those for the 400 and 700 mg/m^2 dose levels. A linear relationship for AUC_{0-t} for the every-second-week 400, 500 and 600 mg/m^2 dosing regimens could be observed whereas half-life, clearance and volume of distribution remained at constant levels. However, relevant differences in PK behaviour were observed at the 700 mg/m^2 every-second-week dose level. Globally, these data indicate that the closest PK match to the weekly standard regimen will be provided by every-second-week administration of 500 or 600 mg/m^2, with 500 mg/m^2 being the dose of choice on this schedule in terms of convenience and feasibility.

The essential equivalence of standard weekly and every-second-week administration was further indicated by the functional data derived from immunohistochemical analysis in patient skin biopsies of the baseline to week 4 changes in expression level of a panel of proteins associated with EGFR signalling (data not shown). No relevant differences in the change in the levels were apparent between the weekly and every-second-week cetuximab schedules, at any of the tested dose levels.

In conclusion, this study has demonstrated that cetuximab can safely be administered as first-line therapy for patients with mCRC at a once every-second-week dose of 400–700 mg/m^2, both as a single agent and in combination with the standard irinotecan-based chemotherapy schedule FOLFIRI. PK exposure data indicate that the 500 mg/m^2 dose mirrors most closely standard weekly administration of cetuximab and is therefore the dose of choice in this schedule for future studies.

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