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Cediranib with mFOLFOX6 *vs* bevacizumab with mFOLFOX6 in previously treated metastatic colorectal cancer

D Cunningham*[,1], R P W Wong[2], G D'Haens[3,4], J-Y Douillard[5], J Robertson[6], A M Stone[6] and E Van Cutsem[7] on behalf of the HORIZON I study group

[1]*Medical Oncology, Royal Marsden Hospital, 15 Cotswold Road, Sutton, Surrey SM2 5NG, UK;* [2]*CancerCare Manitoba, St Boniface General Hospital, 409 Tachè Avenue, Winnipeg, Manitoba, Canada R2H 2A6;* [3]*Academic Medical Center, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands;* [4]*Imelda GI Clinical Research Center, Imeldalaan 9, Bonheiden B-2820, Belgium;* [5]*Institut de Cancerologie de l'Ouest (ICO) R Gauducheau, Bld Jacques Monod, St Herblain 44805, France;* [6]*AstraZeneca, Alderley Park, Macclesfield SK10 4TG, UK and* [7]*University Hospital Gasthuisberg, Leuven 3000, Belgium*

Background: Cediranib is a highly potent inhibitor of vascular endothelial growth factor (VEGF) signalling with activity against all three VEGF receptors. Bevacizumab is an anti-VEGF-A monoclonal antibody with clinical benefit in previously treated metastatic colorectal cancer (mCRC).

Methods: Patients with mCRC who had progressed following first-line therapy were randomised 1 : 1 : 1 to modified (m)FOLFOX6 plus cediranib (20 or 30 mg day^{-1}) or bevacizumab (10 mg kg^{-1} every 2 weeks). The primary objective was to compare progression-free survival (PFS) between treatment arms.

Results: A total of 210 patients were included in the intent-to-treat (ITT) analysis (cediranib 20 mg, $n = 71$; cediranib 30 mg, $n = 73$; bevacizumab, $n = 66$). Median PFS in the cediranib 20 mg, cediranib 30 mg and bevacizumab groups was 5.8, 7.2 and 7.8 months, respectively. There were no statistically significant differences between treatment arms for PFS (cediranib 20 mg *vs* bevacizumab: HR = 1.28 (95% CI, 0.85–1.95; $P = 0.29$); cediranib 30 mg *vs* bevacizumab: HR = 1.17 (95% CI, 0.77–1.76; $P = 0.79$)) or overall survival (OS). Grade $\geqslant 3$ adverse events were more common with cediranib 30 mg (91.8%) *vs* cediranib 20 mg (81.4%) or bevacizumab (84.8%).

Conclusion: There were no statistically significant differences between treatment arms for PFS or OS. When combined with mFOLFOX6, the 20 mg day^{-1} dose of cediranib was better tolerated than the 30 mg day^{-1} dose.

Colorectal cancer (CRC) is the third most common malignancy in men and second in women worldwide; in 2008, there were an estimated 600 000 deaths attributed to the disease (Ferlay *et al*, 2010). Outcomes for patients with metastatic CRC (mCRC) have been improved by the addition of oxaliplatin (de Gramont *et al*, 1997) and irinotecan (Cunningham *et al*, 1998; Andre *et al*, 1999) to fluorouracil (5-FU) chemotherapy. Both FOLFOX and FOLFIRI have become established first-line regimens; both are also active as second-line therapies, although results from a comparative phase III study, which evaluated the efficacies of FOLFOX and FOLFIRI as first- and second-line therapies in patients with mCRC, showed that clinical benefit was greatly reduced with second-line treatment (median progression-free survival (PFS): 2.5 and 4.2 months for FOLFIRI and FOLFOX, respectively, *vs* 8.5 and 8.0 months for FOLFIRI and FOLFOX, respectively, in the first-line setting; Tournigand *et al*, 2004). In a separate study, third-line FOLFIRI

*Correspondence: Professor D Cunningham; E-mail: David.Cunningham@rmh.nhs.uk
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treatment achieved a response rate of 6%, with a median PFS of 18 weeks, in heavily pretreated patients who had previously received FOLFOX (Cunningham *et al*, 1998; Andre *et al*, 1999). More effective treatment options are needed for the treatment of progressive mCRC.

Targeting the vascular endothelial growth factor (VEGF) signalling axis is a clinically validated therapeutic strategy in patients with advanced mCRC (Cunningham *et al*, 2010). In previously treated patients, the addition of bevacizumab (a monoclonal antibody against VEGF-A) to 5-FU-based (oxaliplatin, leucovorin and fluorouracil) chemotherapy has demonstrated a survival benefit (Giantonio *et al*, 2007). Cediranib is an oral and highly potent VEGF signalling inhibitor with activity against all three VEGF receptor tyrosine kinases and platelet-derived growth factor receptor (Wedge *et al*, 2005). Unlike bevacizumab, which only targets VEGF-A-driven activation of VEGFR-1 and -2, cediranib acts directly at the intracellular receptor tyrosine kinase of VEGFR-1, -2 and -3 and therefore has the potential to inhibit all VEGFR-dependent signalling. Data from early clinical trials in patients with advanced solid tumours have demonstrated that cediranib was generally well tolerated as monotherapy at doses $\leqslant 45\,mg\,day^{-1}$ (Drevs *et al*, 2007; Batchelor *et al*, 2007; Langenberg *et al*, 2008; Yamamoto *et al*, 2009; Matulonis *et al*, 2009; Fiedler *et al*, 2010), and in combination with various anticancer agents (including FOLFOX) at doses up to and including $30\,mg\,day^{-1}$ (Laurie *et al*, 2008; Chen *et al*, 2009; Goss *et al*, 2009, 2010; van Cruijsen *et al*, 2010; LoRusso *et al*, 2011).

This randomised, double-blind, phase II study compared cediranib plus modified (m)FOLFOX6 with bevacizumab plus mFOLFOX6 in patients with mCRC who had progressed following first-line therapy (HORIZON I; study code 2171L0041; NCT00278889).

MATERIALS AND METHODS

Patients. This study was conducted in adult patients with carcinoma of the colon or rectum. Patients were included if they had histologically or cytologically confirmed mCRC, with one or more measurable lesions $\geqslant 10$ mm in the longest diameter by spiral computed tomography, or 20 mm with conventional techniques, according to Response Evaluation Criteria In Solid Tumours (RECIST version 1.0). Patients were also required to have received one prior systemic therapy for mCRC with documented progression during or following therapy, have a World Health Organisation (WHO) performance status of 0–2 and a life expectancy of $\geqslant 12$ weeks.

The main exclusion criteria were any unresolved toxicity, defined as Common Toxicity Criteria (CTC) grade >2 from previous treatments, therapy with oxaliplatin in the previous 12 months, prior VEGF-inhibitor therapy, other concomitant anticancer therapy, a history of uncontrolled hypertension or unstable brain or meningeal metastases, any evidence of severe or uncontrolled systemic diseases, inadequate bone marrow reserve and recent major surgery. Pregnant or breastfeeding women were also excluded. All patients provided written informed consent.

Study design. Patients were randomised in a blinded manner to one of the following treatment groups: mFOLFOX6 + oral cediranib $20\,mg\,day^{-1}$, mFOLFOX6 + oral cediranib $30\,mg\,day^{-1}$ or mFOLFOX6 + intravenous (i.v.) infusion of bevacizumab $10\,mg\,kg^{-1}$ every 2 weeks. All patients received mFOLFOX6 (oxaliplatin $85\,mg\,m^{-2}$ plus leucovorin $400\,mg\,m^{-2}$ i.v. over 2 h, day 1; followed by 5-FU $400\,mg\,m^{-2}$ bolus, day 1; and $2400\,mg\,m^{-2}$ continuous i.v. infusion over 46 h) every 2 weeks. Patients randomised to either cediranib arm also received saline (i.v. infusion every 2 weeks) as a bevacizumab placebo, whereas patients randomised to the bevacizumab arm also received a once-daily oral cediranib placebo tablet. Study treatment continued for an indefinite period until the occurrence of toxicity or withdrawal of patient consent. Patients in all treatment groups could continue with blinded study treatment after progression; patients with disease progression were also offered standard treatment according to local practice.

The cediranib doses for this study were selected based on data obtained from a phase I dose-escalation study (NCT00501605), which indicated that cediranib is biologically active at doses $\geqslant 20\,mg\,day^{-1}$ and was well tolerated at doses up to and including $45\,mg\,day^{-1}$ (Drevs *et al*, 2007). In a phase I combination study (NCT00502060), the addition of cediranib to gefitinib was well tolerated at doses up to and including $30\,mg\,day^{-1}$ (van Cruijsen *et al*, 2010). In addition, data from two other phase I studies of cediranib in combination with chemotherapy (NCT00502567 and NCT00107250) indicate that the AE profiles of cediranib up to and including $45\,mg\,day^{-1}$ doses are similar to those observed in monotherapy studies (Laurie *et al*, 2008; LoRusso *et al*, 2011). The AE profile described for cediranib $30\,mg\,day^{-1}$ in combination with FOLFOX is consistent with the known profile for FOLFOX (LoRusso *et al*, 2011), indicating that this cediranib dose is well tolerated.

The study protocol was approved by the relevant institutional ethical committees and/or review boards. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and the AstraZeneca policy on Bioethics (AstraZeneca, 2011).

Study objectives. The primary objective was to compare the efficacy of cediranib in combination with mFOLFOX6 with that of bevacizumab in combination with mFOLFOX6 by assessment of PFS. Secondary objectives included assessments of objective response rate (ORR), overall survival (OS), safety and tolerability, and health-related quality of life (QoL; methodology and data are presented in Supplementary Section). Exploratory objectives included biomarker analysis (methodology and data are presented in Supplementary Section) and a comparison of treatment effects on best change in tumour size.

Assessments. Tumours were evaluated according to RECIST version 1.0 (Therasse *et al*, 2000). Baseline tumour assessments were performed no more than 4 weeks before the start of study treatment. Follow-up assessments were made at 8-week intervals until week 24 and subsequently every 12 weeks until disease progression or death. The OS data were immature at the primary data cutoff (November 2007) and a follow-up analysis was conducted at a second data cutoff (30 January 2009); OS data from the follow-up analysis are reported here. No other efficacy end points were updated at this time.

Blood pressure, heart rate, haematology and clinical chemistry parameters were all measured every 2 weeks, and electrocardiograms (ECGs) performed when clinically indicated, throughout the treatment period. Adverse events (AEs) were recorded throughout the study and graded according to the National Cancer Institute Common Terminology Criteria (NCI–CTC) version 3.0. An independent data monitoring committee was responsible for interim safety reviews.

Statistical methods. The study was powered to provide sufficient precision in the estimation of the relative rate of progression between the two cediranib groups and the bevacizumab group. Approximately 200 patients were to be recruited. The analysis of PFS was planned to occur when at least 120 progression events had occurred. Assuming that the 120 events occurred equally within each treatment group, it was estimated that the 95% confidence interval (CI) for the hazard ratio (HR) for the comparison of each cediranib group with the bevacizumab group would be within 55%

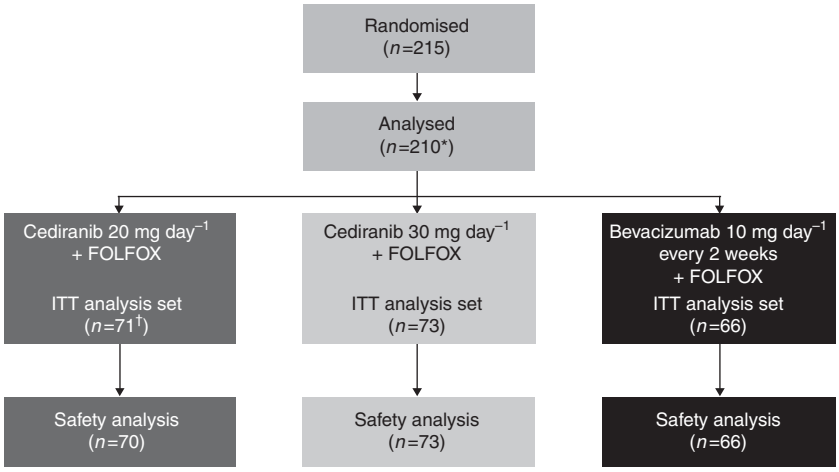


Figure 1. Analysis populations. *Five patients were not included in the intent-to-treat (ITT) analysis because of errors in the assignment of randomised treatment. †One patient in the cediranib 20 mg day^{-1} group was randomised but did not receive study treatment (included in the ITT analysis).

of the point estimate (assuming HR = 1, the corresponding 95% CIs would be 0.65 and 1.55).

The PFS was the time from randomisation to the date of objective progression or death in the absence of objective progression. PFS was analysed on an intent-to-treat (ITT) basis using a log-rank test (Mantel, 1966) stratified by performance status (0 or 1/2), baseline albumin (<4 or $\geqslant 4$ g dl^{-1}) and baseline alkaline phosphatase (ALP; $\leqslant 160$ or >160 U l^{-1}); the *P*-value of the effect of cediranib *vs* bevacizumab treatment was estimated from these models. Treatment effect was estimated by the adjusted HR (95% CI), calculated from the Cox proportional hazards model (Cox, 1972) adjusted using the same baseline covariates as for the log-rank test. If treatment effects were found to be significant, an attempt to determine the cause and type of interaction was to be performed. If the interaction was found to be quantitative, the interaction terms were to be removed and the model refitted, whereas if the interaction was qualitative, the extent of interaction would be assessed by estimating the HR for different values of the covariate. Patients who were lost to follow-up, or had not progressed and were still alive at the time of analysis, were censored at the date of their last evaluable tumour assessment. Overall survival was the time from randomisation to the date of patient death (any cause). Overall survival and time to worsening of QoL were analysed as for PFS. Tumour size was the sum of the longest diameters of the target lesions; the mean duration of response was estimated by assuming a log-logistic distribution. All patient-reported outcomes data were analysed on an ITT basis subject to rules of evaluability.

RESULTS

Patients. Between 4 January 2006 and 12 June 2007, 215 patients were randomised from 42 centres across 10 countries in Europe and Canada (Figure 1). Five patients were excluded from the ITT analysis because of errors in the assignment of randomised treatment. One patient in the cediranib 20 mg day^{-1} group was randomised but did not receive study treatment; nevertheless, that patient was included in the ITT population. There was a greater proportion of patients with a WHO performance status of 0 in the bevacizumab group (72.7%) than in the two cediranib groups (20 mg, 59.2%; 30 mg, 60.3%; Table 1). However, the primary statistical analysis was adjusted for imbalances in performance status. The bevacizumab group had a greater proportion of younger patients, patients with a longer time from diagnosis and patients with rectal cancer. However, additional statistical analyses were undertaken correcting for these imbalances and they were found to have no qualitative effect on the efficacy conclusions.

Efficacy

Progression-free survival. Progression-free survival data were recorded at the initial data cutoff in November 2007. Median PFS in the cediranib 20 and 30 mg groups was 5.8 and 7.2 months, respectively, compared with 7.8 months in the bevacizumab group (Figure 2A). There were no statistically significant differences in the treatment comparisons for PFS; the HR for the comparison between cediranib 20 mg and bevacizumab was 1.28 (95% CI, 0.85–1.95; two-sided $P = 0.29$) and 1.17 (95% CI, 0.77–1.76; two-sided $P = 0.79$) for cediranib 30 mg and bevacizumab.

Subgroup analysis of PFS. A global interaction test to determine the existence of any association between treatment type and baseline covariates (performance status, baseline albumin and baseline ALP) indicated some heterogeneity in treatment effects across subgroups. Further prespecified analysis to determine the cause and type of interaction was performed, revealing an interaction between treatment and high baseline ($>1.5\times$ upper limit of normal) lactate dehydrogenase (LDH) that was significant at the prespecified 10% level ($P = 0.06$; Figure 2B). Of the patients with high baseline LDH, those randomised to cediranib 20 mg showed a slower rate of progression than those randomised to bevacizumab (HR = 0.61; 95% CI, 0.17–2.16), but this trend was not replicated for the cediranib 30 mg *vs* bevacizumab comparison.

No significant interaction was observed between treatment and baseline serum VEGF ($P = 0.46$), or between treatment and the baseline factors used to stratify the primary statistical analysis (baseline albumin, $P = 0.2$; baseline ALP, $P = 0.56$ and WHO performance status, $P = 0.67$).

Overall survival. At the time of the final data cutoff (30 January 2009), 148 (70.5%) patients had died. There was no statistically significant difference between either of the cediranib groups and the bevacizumab group: HR 1.39 (95% CI, 0.92–2.09; $P = 0.10$) for cediranib 20 mg *vs* bevacizumab; HR 1.00 (95% CI, 0.66–1.50; $P = 0.88$) for cediranib 30 mg *vs* bevacizumab (Figure 2C). Median survival times were 14.3 months, 16.8 months and 19.6 months in the cediranib 20 mg, cediranib 30 mg and bevacizumab groups,

Table 1. Demographic and baseline characteristics

Characteristic	Cediranib 20 mg + mFOLFOX6 (*n* = 71)	Cediranib 30 mg + mFOLFOX6 (*n* = 73)	Bevacizumab 10 mg kg^{-1} + mFOLFOX6 (*n* = 66)
Age, years, *n* (%)			
⩾16–64	31 (44)	32 (44)	43 (65)
⩾65–74	32 (45)	34 (47)	13 (20)
⩾75	8 (11)	7 (10)	10 (15)
Sex, *n* (%)			
Male	49 (69)	47 (64)	39 (59)
Female	22 (31)	26 (36)	27 (41)
Race, *n* (%)			
Caucasian	67 (94.4)	70 (95.9)	63 (95.5)
Black	0 (–)	2 (2.7)	2 (3.0)
Oriental	1 (1.4)	1 (1.4)	0 (–)
Other	3 (4.2)	0 (–)	1 (1.5)
WHO PS, *n* (%)			
0	42 (59)	44 (60)	48 (73)
1	27 (38)	27 (37)	16 (24)
2	2 (3)	2 (3)	2 (3)
Cancer type, *n* (%)			
Colon	50 (70)	51 (70)	38 (58)
Rectal	21 (30)	22 (30)	28 (42)
Time from initial diagnosis to randomisation, months, *n* (%)			
<6	5 (7)	5 (7)	6 (9)
6–12	22 (32)	23 (32)	12 (19)
>12	41 (60)	43 (61)	46 (72)
Missing	3	2	2
Prior therapies, *n* (%)[a]			
Chemotherapy	70 (100)	73 (100)	65 (100)
Radiotherapy	16 (22.9)	14 (19.2)	15 (23.1)
Other[b]	1 (1.4)	0 (–)	1 (1.5)
Baseline LDH[a]			
LDH ⩽1.5 × ULN	49 (71.0)	55 (75.3)	54 (83.1)
LDH >1.5 × ULN	20 (29.0)	18 (24.7)	11 (16.9)

Abbreviations: LDH = lactate dehydrogenase; ULN = upper limit of normal; WHO PS; World Health Organisation performance status.
[a]Proportions of patients were calculated for patients with data available (not the intent-to-treat (ITT) analysis set).
[b]One patient in the cediranib 20 mg arm and one patient in the bevacizumab arm received cetuximab.

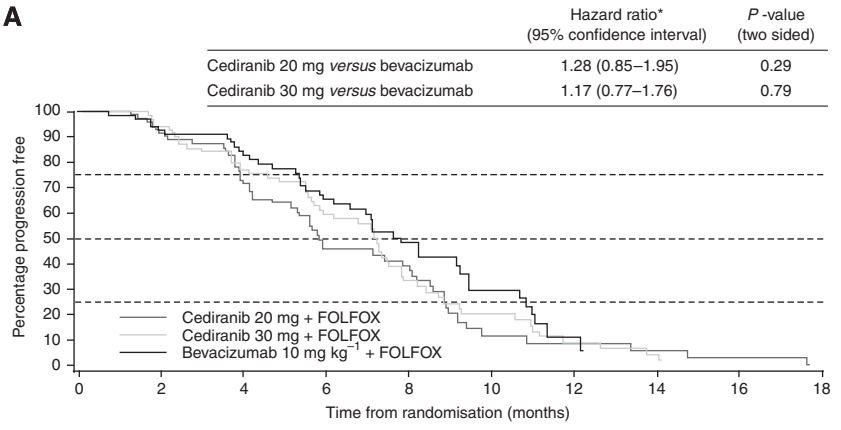
respectively. These median values are not corrected for the more favourable prognosis in the bevacizumab group.

Objective tumour response. In total, 45 patients achieved confirmed RECIST partial responses and were classed as responders (Table 2). Among the responding patients, the mean duration of response was 7.4, 6.3 and 7.8 months in the cediranib 20 mg, cediranib 30 mg and bevacizumab groups, respectively.

The predefined exploratory objective of change in tumour size for each patient at the 8-week assessment was at least as good in the cediranib groups as that seen in the bevacizumab group (Figure 3), although this was not maintained and did not translate into an increased number of patients with a confirmed response.

Safety and tolerability. At the time of the final data cutoff (30 January 2009), the median durations of cediranib/cediranib placebo treatment were shorter in the cediranib groups (150 days in the cediranib 20 mg group and 163 days in the cediranib 30 mg group) compared with the bevacizumab group (190 days). Dose reductions of cediranib/cediranib placebo were highest in the cediranib 30 mg group (37.0% *vs* 12.9% and 12.1% in the cediranib 20 mg and bevacizumab groups, respectively); similar proportions of patients experienced dose pauses in each group, with patients requiring one or two pauses. For bevacizumab/bevacizumab placebo treatment, patients received a median of 8.5, 8.0 and 12.0 cycles in the cediranib 20 mg, cediranib 30 mg and bevacizumab groups, respectively; dose reductions were highest in the cediranib 30 mg group (21.9% *vs* 11.4% in the cediranib 20 mg group and 10.6% in the bevacizumab group). Patients receiving bevacizumab received a higher number of mFOLFOX6 cycles and achieved a higher dose intensity over the first 3 months of the study than patients receiving cediranib (Figure 4). More patients in the bevacizumab group remained on randomised therapy compared with those in the cediranib groups.

In all groups, the most common AEs were diarrhoea, fatigue, nausea and hypertension (Table 3). Diarrhoea was reported more

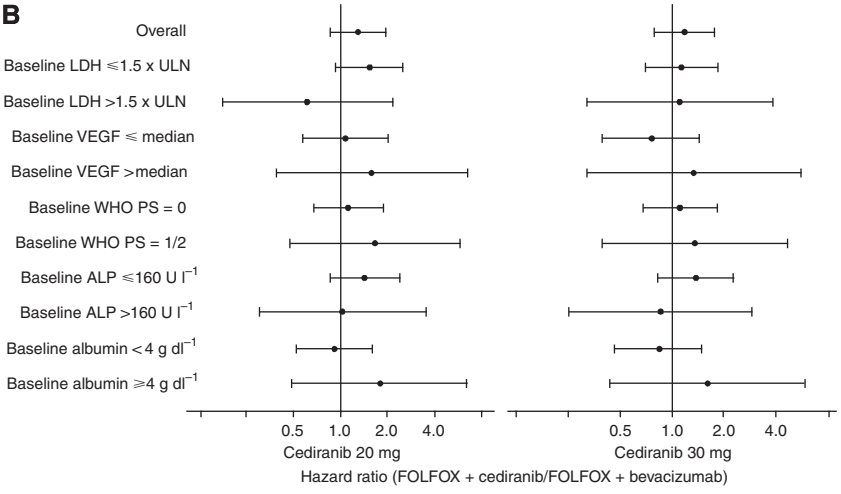


	Hazard ratio* (95% confidence interval)	*P*-value (two sided)
Cediranib 20 mg *versus* bevacizumab	1.28 (0.85–1.95)	0.29
Cediranib 30 mg *versus* bevacizumab	1.17 (0.77–1.76)	0.79

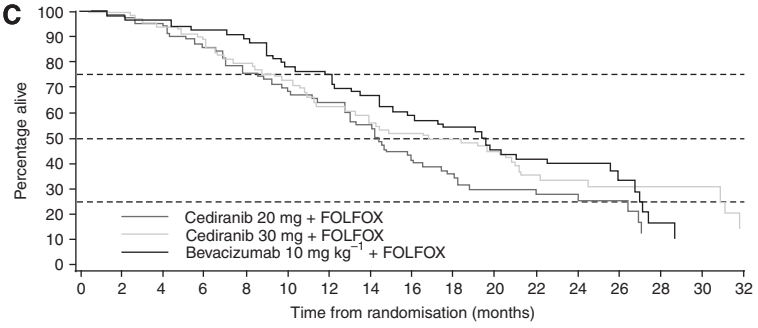
Number of patients at risk†

Months	0	2	4	6	8	10	12	14	16	18
Cediranib 20 mg + FOLFOX	71	63	46	23	19	4	3	2	1	0
Cediranib 30 mg + FOLFOX	73	66	52	34	16	9	4	2	1	1
Bevacizumab 10 mg kg^{-1} + FOLFOX	66	59	50	35	19	9	2	0	0	0

*Hazard ratio <1 favours cediranib. †The number of patients at risk denotes the number of patients progression-free at the beginning of the period. Dashed horizontal lines in Kaplan–Meier plot indicate median and quartiles.



Abbreviations: ALP = alkaline phosphatase; LDH = lactate dehydrogenase; ULN = upper limit of normal; VEGF = vascular endothelial growth factor; WHO PS = World Health Organisation performance status. Hazard ratios <1 favour cediranib.



Number of patients at risk*

Months	0	4	8	12	16	20	24	28	32
Cediranib 20 mg + FOLFOX	71	66	53	45	29	19	11	3	2
Cediranib 30 mg + FOLFOX	73	67	56	43	36	31	14	10	3
Bevacizumab 10 mg kg^{-1} + FOLFOX	66	62	57	48	38	28	15	4	1

*The number of patients at risk denotes the number of patients alive at the beginning of the period. The Kaplan–Meier curve is presented up until the last event. Dashed horizontal lines in Kaplan–Meier plot indicate median and quartiles.

Figure 2. Efficacy results. (**A**) progression-free survival; (**B**) subgroup analysis of progression-free survival; (**C**) overall survival.

frequently in the cediranib groups compared with the bevacizumab group. Hypertension occurred most frequently in the cediranib 30 mg group; hypertensive crisis was reported in one patient in the cediranib 20 mg group and two patients in the cediranib 30 mg group. Rates of reported neutropenia were similar in the cediranib 30 mg group and the bevacizumab group (44% *vs* 46%,

Table 2. Objective response rate (ITT analysis set evaluable for RECIST)

	Number (%) of patients		
Best overall response	**Cediranib 20 mg + mFOLFOX6 (*n* = 71)**	**Cediranib 30 mg + mFOLFOX6 (*n* = 73)**	**Bevacizumab 10 mg kg^{-1} + mFOLFOX6 (*n* = 66)**
Responders	13 (18.3)	14 (19.2)	18 (27.3)
CR	0 (–)	0 (–)	0 (–)
PR[a]	13 (18.3)	14 (19.2)	18 (27.3)
Stable disease[b]	36 (50.7)	44 (60.3)	38 (57.6)
Unconfirmed partial response[c]	9 (12.7)	8 (11.0)	3 (4.5)
Progressive disease	19 (26.8)	12 (16.4)	9 (13.6)
Non-evaluable	3 (4.2)	3 (4.1)	1 (1.5)

Abbreviations: ITT = intent-to-treat; RECIST = Response Evaluation Criteria In Solid Tumours; CR = complete response; PR = partial response.
[a]PRs were classed as confirmed if the response was ongoing at a subsequent assessment at least 4 weeks from when the response was first observed.
[b]Recorded on or after 14 weeks following randomisation.
[c]PRs were classed as unconfirmed if the response was not observed at assessments subsequent to when the response was first observed.

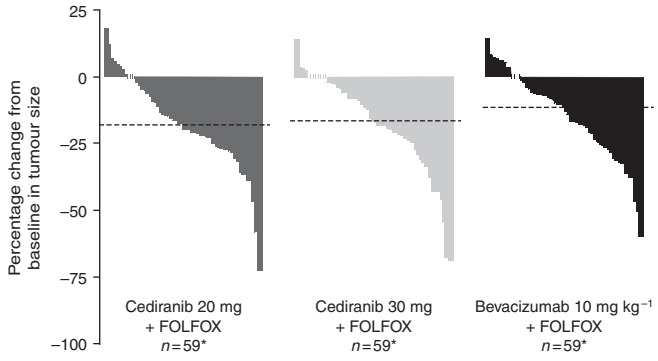


Figure 3. Change in tumour size at the first scheduled assessment following 8 weeks of treatment. **n* represents the number of patients with target lesion data at 8 weeks. Dashed line represents the median change in tumour size. Each bar represents one patient.

respectively). Common Terminology Criteria for Adverse Events (CTCAEs) grade ⩾3 were more common in the cediranib 30 mg group (91.8%) than the cediranib 20 mg group (81.4%) or the bevacizumab group (84.8%). Serious AEs were also more common in the cediranib 30 mg group (53.4%) than the cediranib 20 mg (42.9%) or bevacizumab (43.9%) groups. More patients in the cediranib groups reported AEs leading to discontinuation of cediranib/cediranib placebo compared with the bevacizumab group (cediranib 20 mg: 34.3%; cediranib 30 mg: 45.2%; and bevacizumab: 25.8%).

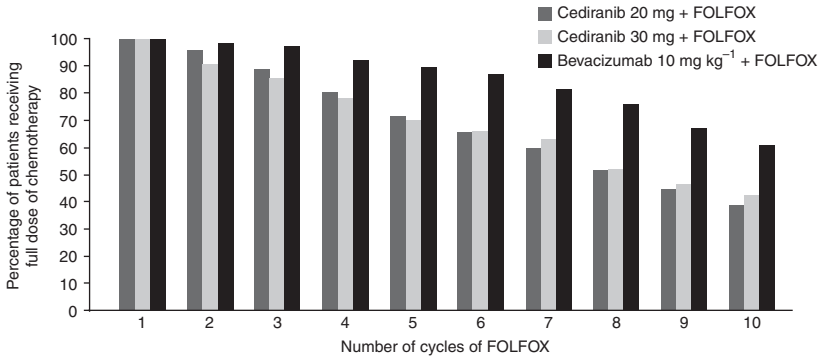
The 'all-cause' 60-day mortality rate was 3.8%. Five deaths attributed to AEs occurred during the treatment period or within 30 days of the last dose of investigational therapy: $n = 1$, cediranib 20 mg group (anastomotic ulcer); $n = 2$, cediranib 30 mg group (sudden cardiac death; haemorrhage); and $n = 2$, bevacizumab group (pulmonary embolism; hepatic failure).

For haematology parameters, no changes in red blood cells or coagulation parameters were observed. There was a reduction in platelets throughout the study in all groups; this was slightly greater in the cediranib 30 mg group. The pattern of change in mean and median values was similar across groups. Within each group, there was a decrease in neutrophil count from day 7 that remained unchanged over time. For laboratory tests, increases in thyroid-stimulating hormone (TSH) were most marked in the cediranib 30 mg group; increases in TSH did not lead to reductions in free thyroxine (T4) or free triiodothyronine (T3). Slight increases in alanine transaminase, aspartate transaminase and bilirubin were more common in the cediranib groups than the bevacizumab group, but the values were within the normal range. Blood pressure, heart rate and ECG findings for all treatment groups were consistent with previous clinical trial experience.

DISCUSSION

This study (HORIZON I) was part of the wider HORIZON programme of clinical investigation, which included two larger phase III studies (HORIZON II and HORIZON III; Hoff *et al*, 2012; Schmoll *et al*, 2012) in a first-line treatment setting. In this phase II study in second-line mCRC, there were no statistically significant differences in PFS between patients treated with cediranib in combination with mFOLFOX6 and patients treated with bevacizumab in combination with mFOLFOX6, but median PFS was longest in the bevacizumab group. Patients enroled in this study were representative of the target population; the only possible exception was a higher proportion of patients with a WHO performance status of 0 compared with similar studies (Giantonio *et al*, 2007; Van Cutsem *et al*, 2011b).

The PFS outcomes for bevacizumab were consistent with an earlier study of this agent in combination with mFOLFOX6 chemotherapy in previously treated patients (median 7.8 months in the present study *vs* 7.2 months; Giantonio *et al*, 2007). The median PFS data for cediranib (20 mg, 5.8 months; 30 mg, 7.2 months) in this second-line setting are favourable when compared with mFOLFOX6 alone (4.1 months; Giantonio *et al*, 2007) and comparable to that observed with the VEGF receptor tyrosine kinase inhibitor vatalanib (PTK787/ZK 222584) in combination with mFOLFOX6 (5.6 months; Van Cutsem *et al*, 2011b), and with the anti-VEGF-A and -B inhibitor aflibercept in combination with FOLFIRI (6.9 months; Van Cutsem *et al*, 2011a). In contrast to the overall PFS analysis, patients with high baseline LDH levels treated with cediranib 20 mg had a longer PFS than those treated with bevacizumab; however, this finding was based on only 18 and 10 progression events in the cediranib 20 mg and bevacizumab arms, respectively, and was not replicated in the higher cediranib dose group. As such, definitive conclusions cannot be made. However, findings from the vatalanib study suggested that there was a trend towards better clinical outcomes in the subgroup of patients with high LDH (Van Cutsem *et al*, 2011b) and,



	Cediranib 20 mg + FOLFOX	Cediranib 30 mg + FOLFOX	Bevacizumab 10 mg kg^{-1} + FOLFOX
Median number of FOLFOX cycles	8	8	11
Median FOLFOX dose intensity over the first 3 months (%)	71	71	85

Figure 4. Chemotherapy dose intensity.

Table 3. Commonly occurring adverse events (⩾20% incidence in any arm; all grades) and CTCAEs grade ⩾3 (with an overall frequency of >2%)

	Cediranib 20 mg + mFOLFOX6 (*n* = 70)		Cediranib 30 mg + mFOLFOX6 (*n* = 73)		Bevacizumab 10 mg kg^{-1} + mFOLFOX6 (*n* = 66)	
Adverse event, *n* (%)	**All**	**⩾3**	**All**	**⩾3**	**All**	**⩾3**
Diarrhoea	52 (74)	13 (19)	56 (77)	14 (19)	42 (64)	11 (17)
Fatigue	35 (50)	10 (14)	42 (58)	8 (11)	39 (59)	9 (14)
Nausea	35 (50)	–	41 (56)	–	38 (58)	–
Hypertension	35 (50)	7 (10)	45 (62)	16 (22)	33 (50)	9 (14)
Neutropenia	37 (53)	26 (37)	32 (44)	25 (34)	30 (45)	19 (29)
Anorexia	29 (41)	6 (9)	26 (36)	5 (7)	29 (44)	3 (5)
Stomatitis	22 (31)	1 (1)	34 (47)	5 (7)	25 (38)	4 (6)
Paraesthesia	20 (29)	1 (1)	31 (42)	4 (5)	24 (36)	4 (6)
Vomiting	22 (31)	1 (1)	28 (38)	2 (3)	25 (38)	2 (3)
Thrombocytopenia	26 (37)	4 (6)	29 (40)	8 (11)	15 (23)	0 (0)
Peripheral sensory neuropathy	20 (29)	3 (4)	17 (23)	1 (1)	25 (38)	5 (8)
Abdominal pain	21 (30)	6 (9)	21 (29)	2 (3)	17 (26)	2 (3)
Dysphonia	22 (31)	–	21 (29)	–	13 (20)	–
Constipation	17 (24)	–	14 (19)	–	18 (27)	–
Asthenia	17 (24)	6 (9)	18 (25)	9 (12)	9 (14)	2 (3)
Pyrexia	13 (19)	–	15 (21)	–	16 (24)	–
Headache	11 (16)	–	16 (22)	–	16 (24)	–
Proteinuria	13 (19)	0 (0)	13 (18)	6 (8)	15 (23)	2 (3)
Epistaxis	12 (17)	–	15 (21)	–	13 (20)	–
Weight decreased	17 (24)	–	8 (11)	–	8 (12)	–
Hypertensive crisis	–	1 (1)	–	2 (3)	–	0 (0)
Pulmonary embolism	–	1 (1)	–	1 (1)	–	2 (3)
Hypokalaemia	–	2 (3)	–	3 (4)	–	1 (2)
ALT increased	–	2 (3)	–	3 (4)	–	0 (0)
Dehydration	–	2 (3)	–	2 (3)	–	1 (2)

Abbreviations: CTCAEs = Common Terminology Criteria for Adverse Events; ALT = alanine transaminase.

together with our findings, indicate that high baseline LDH levels may be associated with improved patient outcomes. However, such findings have not been demonstrated in previous studies with bevacizumab (Suenaga *et al*, 2011; Scartozzi *et al*, 2012; Cetin *et al*, 2012). These inconsistencies may indicate that, rather than overall LDH expression, levels of specific isoforms of

LDH may have a predictive influence on clinical outcomes. Indeed, Koukourakis *et al* (2011) recently reported a potential predictive and prognostic role for tumour LDH5 levels in patients with mCRC.

In a predefined analysis, the change in tumour size at 8 weeks was at least as good for patients randomised to cediranib 20 or 30 mg as those randomised to bevacizumab. However, these early response data were not mirrored in the subsequent objective response rates, determined using RECIST version 1.0 (earliest possible confirmed response at 12 weeks); this may be because of the reduced tolerability associated with cediranib and the subsequent reduction in mFOLFOX6 dose intensity. Overall survival did not differ significantly among the three treatment groups, but median OS showed a numerical advantage favouring the bevacizumab group (cediranib 20 mg, 14.3 months; cediranib 30 mg, 16.8 months; and bevacizumab, 19.6 months). Median OS values were not adjusted for differences in baseline characteristics, which potentially explains why the differences in median OS between treatment arms were greater than might be expected from the adjusted HRs. Furthermore, as median OS values are calculated from a single point on the respective Kaplan–Meier plot, they are not always representative of the treatment effect; in the current study, the median OS for the cediranib 20 mg arm in particular is considered to be rather unrepresentative of the overall treatment effect for this arm. The median OS outcomes in all treatment groups in this study were longer than those reported previously for FOLFOX alone in the previously treated setting (10.8 months; Giantonio *et al*, 2007; 11.9 months; Van Cutsem *et al*, 2011b), FOLFOX4 + bevacizumab (12.9 months; Giantonio *et al*, 2007) or FOLFOX4 + vatalanib (13.1 months; Van Cutsem *et al*, 2011b). The median OS in the bevacizumab arm in the current study was similar to that reported previously with bevacizumab plus chemotherapy in previously untreated patients (Saltz *et al*, 2008), although the reasons for this similarity are unclear. Overall, the efficacy results suggest that cediranib is an active agent in second-line mCRC, and efficacy appears to be similar at the 20 mg and 30 mg doses. Of note, only one patient received bevacizumab as a third-line treatment.

The most common AEs reported in cediranib-treated patients were diarrhoea, fatigue, nausea and hypertension, which is consistent with the findings from previous cediranib studies (Drevs *et al*, 2007; Chen *et al*, 2009; Yamamoto *et al*, 2009), and with the safety profiles of other VEGFR tyrosine kinase inhibitors (Llovet *et al*, 2008; Hecht *et al*, 2011; Schutz *et al*, 2011). Patients who received cediranib had more AEs leading to discontinuation of study medication, and received fewer cycles and a lower dose intensity of mFOLFOX6 compared with those in the bevacizumab group; the decreased mFOLFOX6 dose intensity in the cediranib groups may have affected the efficacy outcomes in these treatment arms. The increased number of discontinuations and reduced dose intensity in the cediranib groups were not attributable to one specific AE.

Symptom- and health-related QoL scores showed a numerical, but not statistically significant, advantage favouring the bevacizumab arm. This difference may have been because of the management of diarrhoea, in which randomised treatment and mFOLFOX6 were discontinued if grade 2 diarrhoea, which was more common in patients receiving cediranib, persisted for more than 2 weeks despite loperamide treatment.

The VEGF levels increased in patients treated with cediranib and decreased in those treated with bevacizumab. As the immunoassay used in the study can only measure free VEGF, the apparent decreases in the bevacizumab arm are likely because of VEGF binding to bevacizumab; therefore, it cannot be determined whether total VEGF levels increase or decrease on bevacizumab treatment. However, the data indicate that sufficient bevacizumab was present to bind to most of the VEGF in the blood. The sVEGFR-2 levels in patients treated with bevacizumab did not decrease to the same extent as in patients treated with cediranib. This may be because of the different modes of action of cediranib, which is an inhibitor of VEGFRs, and bevacizumab, which targets the ligand VEGF-A and therefore has no direct influence on VEGFR levels.

In summary, the results of this study show that cediranib (20 mg and 30 mg) has activity in patients with previously treated mCRC, with no statistically significant differences observed in treatment comparisons with bevacizumab for the primary end point of PFS. In combination with mFOLFOX6, the 20 mg dose of cediranib was better tolerated than the 30 mg dose, although patients in both cediranib groups (particularly 30 mg) had a higher frequency of AEs leading to discontinuation than patients in the bevacizumab arm. The experience gained by investigators in this study informed the management of toxicity in the first-line setting (in HORIZON II and III), for example, early and proactive management of mild AEs. In particular, the early use of antidiarrhoeal agents and the use of short (2 to 3 days) cediranib dose interruptions minimised the impact on chemotherapy delivery. However, following completion of the HORIZON clinical trials programme, efficacy data from the HORIZON II and III trials were not considered to be sufficient to warrant continued development of cediranib as a treatment for patients with mCRC (Schmoll *et al*, 2012; Hoff *et al*, 2012).

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CONFLICT OF INTEREST

DC has received research funding from AstraZeneca, Amgen, Roche and Sanofi. J-YD has received remuneration for consulting and/or advisory board from AstraZeneca, Roche, Amgen, Boehringer-Ingelheim, GSK, Merck, Pfizer and Merck-Serono, and research funding from Merck-Serono. JR and AMS are employees of AstraZeneca and own stock. EVC has received research funding from AstraZeneca and Roche (paid at author's institution). GD'H and RPWW declare no conflict of interest.

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