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ORIGINAL REPORT

Cediranib With mFOLFOX6 Versus Bevacizumab With mFOLFOX6 As First-Line Treatment for Patients With Advanced Colorectal Cancer: A Double-Blind, Randomized Phase III Study (HORIZON III)

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ABSTRACT

Purpose
To compare the efficacy of cediranib (a vascular endothelial growth factor receptor tyrosine kinase inhibitor [VEGFR TKI]) with that of bevacizumab (anti–VEGF-A monoclonal antibody) in combination with chemotherapy as first-line treatment for advanced metastatic colorectal cancer (mCRC).

Patients and Methods
HORIZON III [Cediranib Plus FOLFOX6 Versus Bevacizumab Plus FOLFOX6 in Patients With Untreated Metastatic Colorectal Cancer] had an adaptive phase II/III design. Patients randomly assigned 1:1:1 received mFOLFOX6 [oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 intravenously followed by fluorouracil 400 mg/m^2 intravenously on day 1 and then continuous infusion of 2,400 mg/m^2 over the next 46 hours every 2 weeks] with cediranib (20 or 30 mg per day) or bevacizumab (5 mg/kg every 14 days). An independent end-of-phase II analysis concluded that mFOLFOX6/cediranib 20 mg met predefined criteria for continuation; subsequent patients received mFOLFOX6/cediranib 20 mg or mFOLFOX6/bevacizumab (randomly assigned 1:1). The primary objective was to compare progression-free survival (PFS).

Results
In all, 1,422 patients received mFOLFOX6/cediranib 20 mg (n = 709) or mFOLFOX6/bevacizumab (n = 713). Primary analysis revealed no significant difference between arms for PFS (hazard ratio [HR], 1.10; 95% CI, 0.97 to 1.25; $P = .119$), overall survival (OS; HR, 0.95; 95% CI, 0.82 to 1.10; $P = .541$), or overall response rate (46.3% *v* 47.3%). Median PFS and OS were 9.9 and 22.8 months for mFOLFOX6/cediranib and 10.3 and 21.3 months for mFOLFOX6/bevacizumab. The PFS upper 95% CI was outside the predefined noninferiority limit (HR < 1.2). Common adverse events with more than 5% incidence in the cediranib arm included diarrhea, neutropenia, and hypertension. Cediranib-treated patients completed fewer chemotherapy cycles than bevacizumab-treated patients (median 10 *v* 12 cycles). Patient-reported outcomes (PROs) were significantly less favorable in cediranib-treated versus bevacizumab-treated patients ($P < .001$).

Conclusion
Cediranib activity, in terms of PFS and OS, was comparable to that of bevacizumab when added to mFOLFOX6; however, the predefined boundary for PFS noninferiority was not met. The cediranib safety profile was consistent with previous studies but led to less favorable PROs compared with bevacizumab. Investigation of oral TKIs in CRC continues.

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INTRODUCTION

The 2010 International Consensus for colorectal cancer (CRC) treatment acknowledged that bevacizumab, an anti–vascular endothelial growth factor A (VEGF-A) antibody, in combination with FOLFOX/FOLFIRI [infusional fluorouracil (FU), leucovorin, and oxaliplatin/infusional FU, leucovorin, and irinotecan], belongs to standard first-line treatment in CRC.[1] This opinion was based on trials demonstrating the clinical benefit of targeting VEGF signaling in previously untreated metastatic CRC (mCRC) with bevacizumab combined with chemotherapy.[2-4] Although the addition of bevacizumab to

oxaliplatin/fluoropyrimidine-based chemotherapy has shown significant improvements in progression-free survival (PFS) as first-line treatment,[4] an overall survival (OS) benefit has not been demonstrated in first-line treatment.

Cediranib is an oral, highly potent, VEGF tyrosine kinase inhibitor (TKI) with activity against all three VEGF receptors (VEGFRs).[5,6] Early-phase clinical evaluation showed that cediranib is generally well tolerated, with encouraging antitumor efficacy as monotherapy[7-10] and when combined with various anticancer agents.[11-16] A phase I study in patients with untreated mCRC concluded that cediranib 30 mg per day plus mFOLFOX6 [oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 intravenously followed by FU 400 mg/m^2 intravenously on day 1 and then continuous infusion of 2,400 mg/m^2 over the next 46 hours every 2 weeks] was tolerable and warranted further investigation.[12] We report the results of a phase II/III, randomized, double-blind, multicenter study (NCT00384176) that compared the efficacy and tolerability of mFOLFOX6 plus cediranib with mFOLFOX6 plus bevacizumab in patients with previously untreated mCRC. This study (HORIZON III [Cediranib Plus FOLFOX6 Versus Bevacizumab Plus FOLFOX6 in Patients With Untreated Metastatic Colorectal Cancer]) is one of two pivotal phase III studies of cediranib in first-line mCRC; the other, HORIZON II [Cediranib (AZD2171, RECENTIN) in Addition to Chemotherapy Versus Placebo Plus Chemotherpy in Patients With Untreated Metastatic Colorectal Cancer], compared the efficacy of FOLFOX/CAPOX [FOLFOX/capecitabine plus oxaliplatin] plus cediranib with FOLFOX/CAPOX plus placebo.[17,17a]

PATIENTS AND METHODS

Patients

Eligible patients were age ≥ 18 years with histologic or cytologic confirmation of mCRC (stage IV), a WHO performance status (PS) of 0 or 1, and life expectancy ≥ 12 weeks. Any adjuvant or neoadjuvant oxaliplatin or FU therapy must have been completed more than 12 or more than 6 months, respectively, before study entry. Exclusion criteria included any unresolved toxicity of Common Toxicity Criteria (CTC) grade > 2 from previous anticancer therapy (except hematologic toxicity and alopecia) and prior therapy with monoclonal antibodies or small-molecule inhibitors against VEGF and VEGFRs. All patients provided written informed consent. The trial was approved by all relevant institutional ethical committees or review bodies and was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice, and the AstraZeneca policy on bioethics.[18]

Study Design

This phase II/III, randomized, double-blind, adaptive design study was conducted in 206 centers across 28 countries. During the phase II stage, patients were randomly assigned 1:1:1 to receive cediranib 20 or 30 mg day plus bevacizumab-matched placebo, or bevacizumab 5 mg/kg intravenous infusion every 14 days plus cediranib-matched placebo, each combined with 14-day treatment cycles of mFOLFOX6 (day 1: oxaliplatin 85 mg/m^2 intravenously with leucovorin 400 mg/m^2 intravenously over 2 hours, followed by FU 400 mg/m^2 intravenous bolus, and then 2,400 mg/m^2 continuous intravenous infusion over 46 hours). An independent data monitoring committee (IDMC) conducted end-of-phase (EoP) II data analysis (after 225 patients had 3 months of follow-up; data from the HORIZON I [Cediranib Plus FOLFOX6 Versus Bevacizumab Plus FOLFOX6 in Patients With Previously Treated Metastatic Colorectal Cancer] and HORIZON II studies were also included in the analysis. The IDMC concluded that cediranib 20 mg met all predefined criteria for continuation; subsequently, patients enrolled onto the phase III part of this study were randomly assigned 1:1 to receive mFOLFOX6 with cediranib 20 mg or bevacizumab (plus the respective matched placebo). All study personnel other than the IDMC remained blinded to the data until trial end. Predefined criteria for the continuation of these studies included an improvement of more than 10% in the response rate compared with the bevacizumab arm at the EoP II analysis in HORIZON III. Patients who received cediranib 30 mg in the phase II stage were unblinded with the option to continue on open-label cediranib (20 or 30 mg per day). Patients were stratified at random assignment according to two-level liver function covariates (on the basis of baseline albumin < 4 g/dL, ≥ 4 g/dL; alkaline phosphatase ≤ 160 U/L, > 160 U/L)[19] and WHO PS (0, 1). Randomly assigned treatment continued until objective disease progression, unacceptable toxicity, death, withdrawal of patient consent, or other discontinuation criteria.

Study Objectives

The primary objective was to determine the efficacy of cediranib 20 mg plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6 by assessment of PFS. Secondary objectives included comparisons between the two treatment arms for OS, objective response rate (ORR: complete response plus partial response), duration of response (DoR), safety and tolerability, rate of resection of liver metastases (all patients with liver metastases at baseline included), and the effects on health-related quality of life. Exploratory end points included assessments of tumor and blood-based biomarkers, the results of which will be reported separately.

Assessments

PFS was defined as the time from random assignment to the date of objective progression or death. PFS and ORR were determined from objective tumor assessments (by Response Evaluation Criteria in Solid Tumors [RECIST] v1.0), with baseline assessments performed ≤ 4 weeks before the start of study treatment; follow-up assessments occurred at 8-week intervals until week 24 and subsequently every 12 weeks until disease progression or death.

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Disease-related symptoms were assessed by using the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) questionnaire, comprising the FACT-G (general) plus the Colorectal Cancer Subscale (CCS; Appendix, online only).

Statistical Methods

This study was powered to detect a superior PFS (90% power; hazard ratio [HR], 0.80; $\alpha = .05$). If superiority was not achieved, protocol-defined PFS noninferiority required the HR upper 95% CI limit to be less than 1.2. PFS was analyzed on an intention-to-treat basis by using a log-rank test stratified by PS, baseline albumin, and baseline alkaline phosphatase, in accordance with the stratification used at random assignment. For the primary PFS analysis, patients without documented progression events immediately following at least two consecutive missing or nonevaluable RECIST assessments or after commencement of subsequent cancer treatment were censored. Treatment effect was estimated by the HR (95% CI), calculated from a Cox proportional hazards model that was adjusted by using the same baseline covariates as for the log-rank test. Sensitivity analyses included an interval-censored PFS analysis[20] and an analysis based on a blinded central review. OS and time to worsening of disease-related symptoms and health-related quality of life were analyzed as for PFS. Objective response was analyzed via logistic regression by adjusting for the same baseline covariates as for PFS. For responders, the expected DoR was determined by following the methods of Ellis et al[21] with a log-normal distribution assumed to model the time spent in response. This approach avoids bias associated with subset analysis of patients defined by post-treatment outcome who may not be comparable with respect to baseline prognostic factors. The primary analysis was planned when 850 progression events had occurred; an interim assessment of OS was performed at this time, with a final follow-up analysis planned after 950 deaths. No formal statistical analysis was prespecified for safety data.

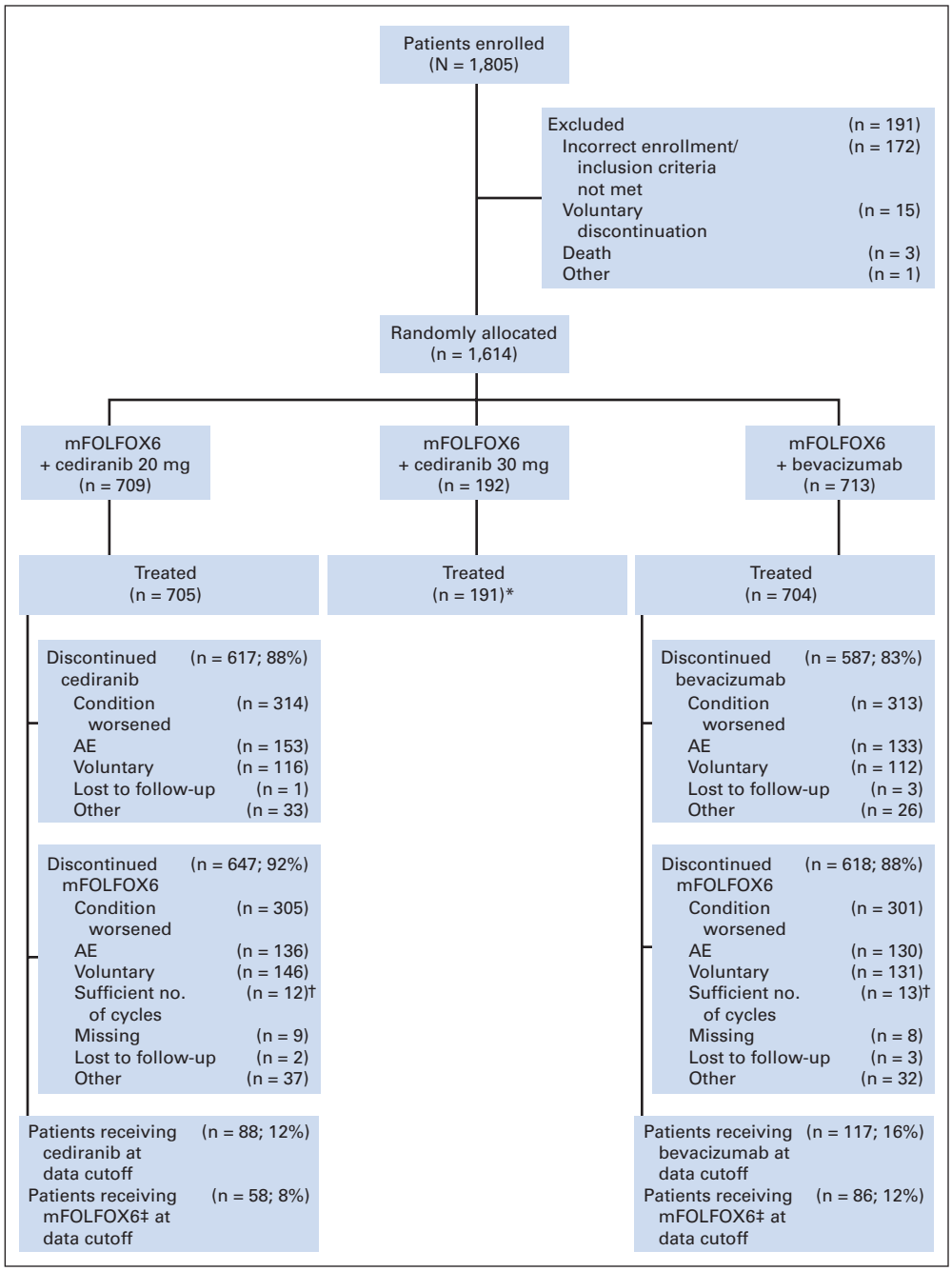

Fig 1. CONSORT diagram. AE, adverse event; mFOLFOX6, oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 intravenously followed by fluorouracil 400 mg/m^2 intravenously on day 1 and then continuous infusion of 2,400 mg/m^2 over the next 46 hours every 2 weeks. (*) Treatment dose stopped after end-of-phase II analysis. (†) In opinion of investigator and in accordance with their local treatment guidelines. (‡) Patients received at least one component of mFOLFOX6.

RESULTS

Patients

Between August 2006 and January 2009, 1,614 patients were randomly assigned to treatment (Fig 1). A total of 226 patients contributed to the EoP II analysis (cediranib 20 mg, n = 74; cediranib 30 mg, n = 76; bevacizumab, n = 76). Recruitment continued during this analysis, with 192 patients randomly assigned to cediranib 30 mg before this arm was stopped. The phase III part of the study comprised 709 patients in the cediranib 20 mg arm and 713 patients in the bevacizumab arm. Patient baseline characteristics were considered representative of the target population[4,22,23] and were generally well balanced between arms (Table 1); a similarly low proportion of patients had received prior adjuvant therapy. The 60-day mortality rate (any cause) between the arms was similar (cediranib, 2.3% [n = 16]; bevacizumab, 1.8% [n = 13]). At data cutoff for the primary analysis (November 15, 2009), 65% of patients (cediranib 20 mg, 66.4% [n = 471]; bevacizumab, 63.5% [n = 453]) had disease progression events, and 34% (cediranib 20 mg, 33.7% [n = 239]; bevacizumab, 34.6% [n = 247]) had died.

Efficacy

The primary end point of PFS showed no significant difference between arms (Fig 2A). The estimated HR was 1.10 (95% CI, 0.97 to

Table 1. Demographic and Baseline Characteristics (intention-to-treat population)

Characteristic	Cediranib 20 mg (n = 709) No.	%	Bevacizumab 5 mg/kg (n = 713) No.	%
Age, years				
Median	59.0		60.0	
Range	18-83		22-88	
Sex				
Male	412	58	414	58
Female	297	42	299	42
WHO performance status				
0	405	57	400	56
1	304	43	312	44
2	0		1	0.1
Type of cancer*				
Colon	464	65	475	67
Rectal	245	35	236	33
Tumor grading				
Well differentiated	68	10	82	12
Moderately differentiated	424	60	418	59
Poorly differentiated	129	18	119	17
Undifferentiated	9	1	2	0.3
Unassessable	60	8	78	11
Unknown	19	3	14	2
Metastatic sites*				
1	304	43	320	45
> 1	405	57	391	55
Metastases at baseline				
Liver only	132	19	158	22
Liver and other metastases	436	61	411	58
No liver involvement	141	20	144	20
Prior adjuvant therapy				
Yes	117	17	138	19
Initial diagnosis to random assignment, months*				
< 6	506	71	498	70
6-< 12	27	4	31	4
12-< 24	56	8	71	10
24-< 36	53	7	51	7
≥ 36	67	9	60	8
Baseline ALP, U/L				
≤ 160	429	61	414	58
> 160	280	39	299	42
Baseline albumin, g/L				
< 40	283	40	266	37
≥ 40	426	60	447	63

Abbreviation: ALP, alkaline phosphatase.
*Information missing for two patients in the bevacizumab group.

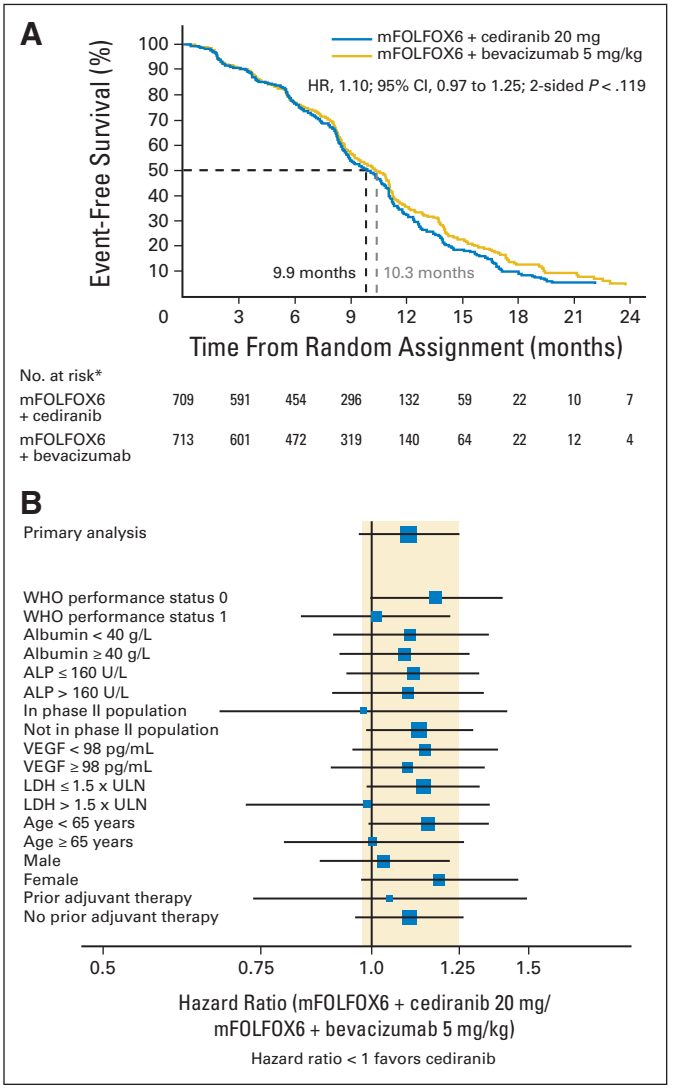

Fig 2. (A) Kaplan-Meier curves of progression-free survival. (B) Subgroup analysis of progression-free survival with respect to baseline assessment of clinical factors. ALP, alkaline phosphatase; HR, hazard ratio; LDH, lactate dehydrogenase; mFOLFOX6, oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 intravenously followed by fluorouracil 400 mg/m^2 intravenously on day 1 and then continuous infusion of 2,400 mg/m^2 over the next 46 hours every 2 weeks; ULN, upper limit of normal; VEGF, vascular endothelial growth factor. NOTE. 98 pg/mL was used as the cutoff to define low and high VEGF subgroups, given that it was the overall median baseline value across HORIZON II [Cediranib (AZD2171, RECENTIN) in Addition to Chemotherapy Versus Placebo Plus Chemotherapy in Patients With Untreated Metastatic Colorectal Cancer] and HORIZON III (Cediranib Plus FOLFOX6 Versus Bevacizumab Plus FOLFOX6 in Patients With Untreated Metastatic Colorectal Cancer). (*) The number of patients at risk denotes the number of patients event free at the beginning of the period.

1.25; $P = .119$); median PFS was 9.9 months (cediranib 20 mg) and 10.3 months (bevacizumab). Because the upper 95% CI was beyond the predefined limit of 1.2, noninferiority of cediranib versus bevacizumab could not be concluded. Analysis of predefined subgroups including baseline lactate dehydrogenase levels did not identify a patient population that derived a differential PFS benefit from either treatment (Fig 2B). Prespecified sensitivity analyses produced results consistent with those of the primary analysis and are not included.

Confirmed ORRs for tumors were comparable between arms (cediranib, 46% [n = 328]; bevacizumab, 47% [n = 337]; Table 2), with no significant difference in ORR (odds ratio, 0.96; 95% CI, 0.77 to 1.18; $P = .672$). The median DoR was 8.6 months (cediranib) and 9.6 months (bevacizumab). There was no statistical difference in the expected DoR (cediranib, 4.65 months; bevacizumab, 5.13 months; $P = .202$).

At the interim OS assessment (median follow-up, 14 months), there was no significant difference between arms (HR, 0.94: 95% CI, 0.79 to 1.12; $P = .546$); median survival was 22.8 months with cediranib versus 21.3 months with bevacizumab. Subgroup analysis at the time of interim assessment revealed no strong evidence of a differential effect in any of the subgroups examined. A final OS analysis was to be conducted at 950

Table 2. Best Objective Response by RECIST

Best Response	Cediranib 20 mg (n = 709) No.	%	Bevacizumab 5 mg/kg (n = 713) No.	%
Responders	328	46	337	47
CR	12	2	11	2
PR	316	45	326	46
Stable disease	259	37	268	38
Progressive disease	82	12	79	11
Nonevaluable	40	6	29	4

Abbreviations: CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

deaths; however, the failure of this study to achieve the PFS noninferiority limit, together with the lack of clinically meaningful benefit in HORIZON II, resulted in an earlier OS analysis when 730 deaths had occurred (cediranib, 357 [50%]; bevacizumab, 373 [52%]). At this final data cutoff, OS remained comparable between the cediranib arm with a median of 22.8 months and the bevacizumab arm with 21.4 months (HR, 0.95; 95% CI, 0.82 to 1.10; $P = .541$; Fig 3).

No distinguishing treatment effects were identified for any of the subgroups analyzed. Following discontinuation of randomly assigned treatment, 28.2% (200 of 709) and 23.8% (170 of 713) of patients randomly assigned to cediranib or bevacizumab, respectively, received postprogression therapy. FOLFIRI was the most common postprogression regimen (cediranib, 72.0% [n = 144]; bevacizumab, 65.9% [n = 112]). Postprogression treatment with bevacizumab and the epidermal growth factor receptor inhibitor cetuximab was balanced across arms. Bevacizumab was given as second-line treatment to 12.5% (n = 25, cediranib) and 12.9% (n = 22, bevacizumab) of patients. Cetuximab was given as second-line or third-line treatment to 4.5% (n = 9) or 14.5% (n = 29) cediranib patients and 4.7% (n = 8) or 13.5% (n = 23) bevacizumab patients, respectively.

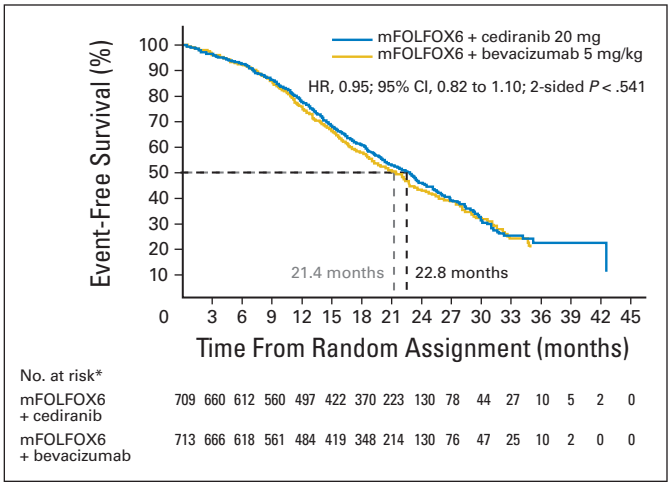

Fig 3. Kaplan-Meier curves for overall survival (final analysis). HR, hazard ratio; mFOLFOX6, oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 intravenously followed by fluorouracil 400 mg/m^2 intravenously on day 1 and then continuous infusion of 2,400 mg/m^2 over the next 46 hours every 2 weeks. (*) The number of patients at risk denotes the number of patients event free at the beginning of the period.

Resection of liver metastases occurred in only 31 patients (4.4%) in the cediranib arm and 37 patients (5.2%) in the bevacizumab arm. For patients with liver-only disease at baseline (cediranib, n = 132; bevacizumab, n = 158), a similar proportion of patients underwent resection from both arms (cediranib, 10.6% [n = 14]; bevacizumab, 13.9% [n = 22]). Because such low numbers of patients underwent resection, the logistic regression model was adjusted for treatment and for whether the patient had liver-only disease at baseline. On the basis of these limited data, no significant difference in the rate of liver resection was found between the treatment arms (odds ratio, 0.89; 95% CI, 0.54 to 1.46; $P = .637$).

Safety and Tolerability

Overall, the median duration of exposure to cediranib was 200 days (range, 1 to 861 days) and to bevacizumab was 210 days (range, 14 to 840 days). Dose reductions or pauses of cediranib/placebo were considered necessary more frequently for patients treated with cediranib (54%, n = 381) compared with patients treated with bevacizumab (36%, n = 258). In the first 6 months of treatment, fewer patients in the cediranib arm completed the planned number of chemotherapy treatment cycles compared with patients in the bevacizumab arm (35% [n = 248] *v* 50% [n = 357], respectively for FU; 27% [n = 192] *v* 42% [n = 301], respectively for oxaliplatin). Post hoc comparative analyses indicated that these differences were significantly different at the $P < .001$ level (continuity corrected χ^2 tests). Overall, the median number of mFOLFOX6 cycles was lower for the cediranib arm than for the bevacizumab arm (12 *v* 14 cycles, respectively, for FU; 10 *v* 12 cycles, respectively, for oxaliplatin).

Common AEs (≥ 20% in either arm; all grades) that occurred with 5% or more higher incidence in the cediranib arm were diarrhea, neutropenia, hypertension, stomatitis, thrombocytopenia, and abdominal pain (Table 3). The less common AEs of palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) and dysphonia also had a 5% or more higher incidence in the cediranib arm. Grade ≥ 3 AEs (77% *v* 67%), serious AEs (39% *v* 33%), and AEs leading to permanent discontinuation of cediranib or bevacizumab (24% *v* 21%) were more common with cediranib compared with bevacizumab, respectively. Neutropenia and diarrhea were the only grade ≥ 3 AEs with a frequency of more than 5% higher in the cediranib arm, whereas no differences in incidence were reported for grade ≥ 3 bleeding (1.3% *v* 1.4%), thromboembolism (8.1% *v* 8.4%), and proteinuria (1.0% *v* 0.9%) in the cediranib and bevacizumab arms, respectively. Interestingly, 1.1% (n = 8) of the bevacizumab-treated patients presented with grade 3 or 4 gastrointestinal perforation, compared with no patients treated with cediranib. At the primary data cutoff, most deaths were due to disease progression (89% for the cediranib arm and 87% for the bevacizumab arm). For AEs with an outcome of death, the overall incidence was the same in both arms (2.7% [cediranib] *v* 3.1% [bevacizumab]; pulmonary embolism (n = 4, all bevacizumab) was the only event reported in more than two patients in either arm.

Patient-Reported Outcomes

Compliance with the FACT-C questionnaire was high across all time points (range, 84% to 98%) and comparable between arms. Time to worsening of symptoms (FCSI [Functional Assessment of Cancer Therapy Colorectal Symptom Index]) was significantly shorter in the cediranib arm, with a median time to worsening of symptoms of 5.6 months, compared with 8.0 months in the bevacizumab arm (HR, 1.36; 95% CI, 1.20 to 1.56; two-sided $P < .001$; Fig 4). Statistically

Table 3. Common Adverse Events (≥ 20% incidence in either arm; all grades)

	mFOLFOX6 + Cediranib 20 mg (n = 705)				mFOLFOX6 + Bevacizumab 5 mg/kg (n = 704)			
	Any Grade		Grade 3/4		Any Grade		Grade 3/4	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Diarrhea	493	70*	97	14*	357	51	41	6
Nausea	359	51	—		350	50	—	
Neuropathy peripheral†	354	50	51	7	356	51	68	10
Fatigue	317	45	55	8‡	299	42	34	5
Neutropenia	306	43*	224	32*	233	33	166	24
Hypertension	296	42*	49	7‡	184	26	29	4
Stomatitis	257	36*	—		187	27	—	
Vomiting	224	32	—		202	29	—	
Thrombocytopenia	190	27*	37	5‡	86	12	18	3
Decreased appetite	179	25	—		160	23	—	
Epistaxis	170	24	—		172	24	—	
Abdominal pain	170	24‡	—		131	19	—	
Paresthesia	157	22	—		158	22	—	
Constipation	148	21*	—		191	27	—	

NOTE. Post hoc comparisons of incidence of events with cediranib versus bevacizumab assessed via a continuity correct χ^2 test with no adjustment for multiplicity.
Abbreviation: mFOLFOX6, oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 intravenously followed by fluorouracil 400 mg/m^2 intravenously on day 1 and then continuous infusion of 2,400 mg/m^2 over the next 46 hours every 2 weeks.
*Indicates $P < .001$.
†Including peripheral sensory neuropathy.
‡Indicates $P < .05$.

significant intertreatment differences favoring bevacizumab were also reported for Trial Outcomes Index (HR, 1.31; $P < .001$), Total FACT Score (HR, 1.29; $P < .001$), and CCS (HR, 1.45; $P < .001$). There was no difference in patient-reported outcomes between patients who had progressed and those who had not progressed or between responders and nonresponders. Among patients who had a worsening FCSI score, worsening in diarrhea was the only individual FCSI item that appeared to be largely different between treatment arms (Appendix; Appendix Table A1, online only).

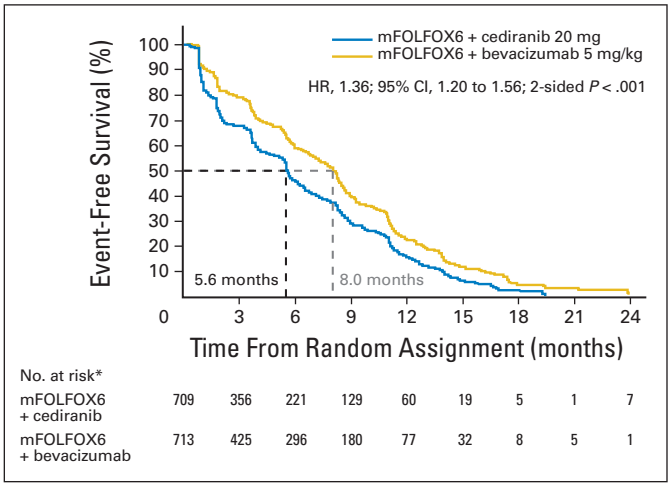

Fig 4. Kaplan-Meier curves for time to worsening of Functional Assessment of Cancer Therapy-Colorectal (FACT-C) symptom index. HR, hazard ratio; mFOLFOX6, oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 intravenously followed by fluorouracil 400 mg/m^2 intravenously on day 1 and then continuous infusion of 2,400 mg/m^2 over the next 46 hours every 2 weeks. (*) The number of patients at risk denotes the number of patients event free at the beginning of the period.

Post Hoc Analysis

Given the observed differences between arms in chemotherapy exposure, a post hoc analysis of PFS was performed in which time-dependent covariates that represented cycles during follow-up during which a patient received component chemotherapy were added to the Cox proportional hazards model. After adjusting for chemotherapy received by using this method, the results suggested that the reduced chemotherapy exposure may have had some impact on overall outcome; however, a small numerical advantage favoring bevacizumab remained (HR, 1.05; 95% CI 0.92 to 1.20).

DISCUSSION

In this randomized phase III study, no statistically significant differences were observed for the primary end point of PFS or the secondary end points (OS, ORR, DoR, rate of liver metastasis resection), between cediranib and bevacizumab when in combination with mFOLFOX6. Furthermore, in contrast to findings that high serum lactate dehydrogenase levels were predictive of improved PFS with vatalanib,[23] no differential PFS benefit was observed in predefined subgroups between arms. This study demonstrated that cediranib 20 mg per day plus mFOLFOX6 has efficacy comparable to that of bevacizumab plus mFOLFOX6 for first-line treatment of mCRC; however, treatment with cediranib did not meet the predefined criteria for noninferiority of PFS versus bevacizumab.

The median PFS achieved in both arms (9.9 months, cediranib; 10.3 months, bevacizumab) is similar to that experienced by patients with previously untreated mCRC receiving bevacizumab plus FOLFOX4/CAPOX [oxaliplatin 85 mg/m^2 intravenously on day 1, leucovorin 200 mg/m^2 per day by intravenous infusion on days 1 and 2, and FU 400 mg/m^2 intravenous bolus followed immediately by 600 mg/m^2 continuous intravenous infusion over 22 hours on days 1 and 2 every 2 weeks/CAPOX] (9.4 months; NO16966 study [A Study of Bevacizumab Plus FOLFOX4/CAPOX As a First-Line Therapy in Patients With Metastatic Colorectal Cancer])[4] or bevacizumab plus mFOLFOX6 (9.9 months; TREE-2 study [Three Regimens of Elotaxin Evaluation]).[24] Our results are also generally consistent with the outcome of the placebo-controlled HORIZON II trial, which achieved its coprimary objective of PFS prolongation with the addition of cediranib 20 mg to FOLFOX/CAPOX (HR, 0.84; $P = .012$; median PFS, 8.6 months with cediranib 20 mg *v* 8.3 months with placebo).[17,17a]

At the final analysis, OS was comparable between the treatment arms. The decision to bring forward the final OS analysis is highly unlikely to have affected the overall outcome; the almost identical OS findings at the interim and final analyses indicate that no divergence was observed in survival times between arms.

No new safety issues were identified with cediranib 20 mg plus mFOLFOX6, and the AE profile was consistent with those of previous cediranib studies.[8,10,12] AEs considered to be related to VEGF signaling inhibition were generally similar in both arms, except for a higher incidence of hypertension in the cediranib arm. However, cediranib was associated with more diarrhea and neutropenia than bevacizumab; these events have been reported for other oral, small-molecule

TKIs.[23,25,26] Most AEs resolved without any impact on cediranib or bevacizumab dosing. However, AEs leading to discontinuation, dose reduction, or dose interruption were reported more frequently for cediranib. All patient-reported outcomes favored bevacizumab plus mFOLFOX6, and this appears to reflect differences in the tolerability profile of each arm, particularly the higher incidence of diarrhea with cediranib treatment, rather than any differential efficacy. Cediranib also appeared to have an effect on chemotherapy delivery: cediranib-treated patients received fewer cycles of mFOLFOX6, which may have contributed to efficacy outcomes. Similarly, the addition of vatalanib to FOLFOX4 in the first-line setting (CONFIRM 1 [Study of FOLFOX4 Plus Vatalanib Versus FOLFOX4 in Patients With Metastatic Colorectal Cancer]) reduced exposure to chemotherapy, probably as a result of increased toxicity compared with the control arm.[23] The incidence of diarrhea was also notable in the vatalanib arm of CONFIRM 1,[23] and it was the most prevalent grade ≥ 3 AE in a phase III study of sunitinib plus FOLFIRI that was stopped at an interim analysis for futility.[27]

In summary, cediranib in combination with mFOLFOX6 showed comparable clinical activity to bevacizumab plus mFOLFOX6 in previously untreated mCRC; however, the predefined boundary for cediranib PFS noninferiority was not met. Overall, cediranib treatment showed a less favorable AE profile compared with bevacizumab, particularly for diarrhea and neutropenia, and this appears to have affected the delivery of chemotherapy. It is not clear why the toxicity profiles were different, although the potential contribution of cediranib activity against non-VEGFR kinases (eg, c-Kit inhibition)[28] cannot be excluded. More generally, the tolerability outcomes of trials (including this study) investigating anti-VEGF/VEGFR strategies suggest that bevacizumab[2-4] (monoclonal antibody) and aflibercept[29] (fusion protein) may be better suited for clinical use than certain TKIs (cediranib[12,17,17a] and vatalanib[23]). However, the potential use of oral VEGFR TKIs continues to be investigated; recent preliminary findings with BIBF1120[30] and regorafenib[31] show promise for treatment of mCRC. These findings, together with our results, show oral VEFGR TKIs, when combined with standard combination chemotherapy, have antitumor activity in CRC. Further investigation with this class of agent is warranted in pursuit of effective clinical treatment. Markers predictive for response to anti-VEGF therapy have not yet been identified but ongoing investigation, in particular, translational biomarker analyses, may reveal benefit in select patient populations.[32] To what extent the partner (irinotecan *v* oxaliplatin) of the fluoropyrimidine-based chemotherapy affects efficacy remains to be established.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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