AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00013
Edition Number	1
Date	1 October 2010

A Randomised, Double-blind, Multicentre Phase II/III Study to Compare the Efficacy of Cediranib (AZD2171) in Combination with 5-fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX), to the Efficacy of Bevacizumab in Combination with FOLFOX in Patients with Previously Untreated Metastatic Colorectal Cancer

Study dates: First subject enrolled: 30 August 2006
Last subject last visit: 2 January 2009

Phase of development: Therapeutic exploratory (II)
Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

During the Phase II part of the study, patients were recruited from approximately 100 centres in Europe, North America and Australia. The Phase III part of the study was designed to enrol additional patients from a further approximately 170 centres in Europe, North and South America, Australia and Asia.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
The efficacy of cediranib in combination with FOLFOX compared to the efficacy of bevacizumab in combination with FOLFOX in patients with previously untreated metastatic CRC.	PFS
Secondary	**Secondary**
The efficacy of cediranib in combination with FOLFOX compared to the efficacy of bevacizumab in combination with FOLFOX in patients with previously untreated metastatic CRC.	OS, ORR (CR + PR), duration of response
The safety and tolerability of randomised study therapies in combination with FOLFOX in patients with previously untreated metastatic CRC.	AEs, laboratory findings (clinical chemistry, haematology, urinalysis), vital signs including BP, physical examination, WHO performance status, ECG
The effects on quality of life (QoL) and disease-related symptoms of cediranib in combination with FOLFOX, compared with the effects of bevacizumab in combination with FOLFOX in patients with previously untreated metastatic CRC.	FACT-C questionnaire, FCSI

In addition, the rate of resection of liver metastases was also measured. This endpoint was not contained within the CSP but was included in the SAP prior to database lock. The rate of resection of liver metastases was reported as an efficacy variable.

Study design

This was a randomised, double blind, international multi centre study that followed an adaptive trial design. The aim of the study was to compare the efficacy of cediranib in combination with modified FOLFOX6 to the efficacy of bevacizumab in combination with modified FOLFOX6, in patients with metastatic CRC.

Adaptive study design

Two cediranib doses (20 mg and 30 mg) were initially included in this study to determine the most appropriate dose for efficacy and tolerability. However, after a planned end-of-Phase II analysis conducted by an external Independent Data Monitoring Committee (IDMC) that

considered pre-specified AstraZeneca criteria relating to tolerability and efficacy, a decision was made to continue with cediranib 20 mg.

Patients who had been randomised to the cediranib 30 mg arm were unblinded and given the option to continue with study treatment on an open-label basis (either to continue with the 30 mg dose or reduce to 20 mg). These patients were to be followed up for PFS and OS. Data from the cediranib dose discontinued at the end of Phase II was not to be included in the final efficacy analyses, but safety information was summarised separately.

Target subject population and sample size

Male and female patients aged ≥18 years with histologically- or cytologically-confirmed Stage IV (metastatic) CRC who have received no prior systemic therapy for metastatic disease. Any adjuvant/neoadjuvant oxaliplatin therapy must have been received >12 months prior to study entry and adjuvant/neoadjuvant 5-FU must have been received >6 months prior to study entry. Patients must not have received prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including bevacizumab and cediranib. Patients must have a World Health Organisation (WHO) performance status of <2 and must have a measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.

Investigational product and comparator(s): dosage and mode of administration

Cediranib (Phase II): to maintain the blind, patients received either one 20 mg tablet plus placebo matching cediranib 30 mg, or one 30 mg tablet plus placebo matching cediranib 20 mg as a once-daily, oral medication. Patients randomised to active bevacizumab received placebo matching cediranib 20 mg and cediranib 30 mg. **Cediranib (Phase III):** to maintain the blind, patients received either one active cediranib 20 mg tablet or a placebo tablet matching cediranib 20 mg. **Bevacizumab:** was to be administered as per standard clinical practice. To maintain the blind, those patients not randomised to bevacizumab 5 mg/kg received bevacizumab placebo (physiological saline). **mFOLFOX6:** All patients were to receive mFOLFOX6 (oxaliplatin 85 mg/m^2 with leucovorin 400 mg/m^2 administered intravenously over 2 hours on Day 1. 5-FU 400 mg/m^2 bolus immediately after completion of the oxaliplatin infusion on Day 1, followed immediately by 5 FU 2400 mg/m^2 administered by a continuous iv infusion over 46 hours), once every 2 weeks.

Duration of treatment

First-line chemotherapy and blinded study medication were to be administered until progression (or other criteria for discontinuation were met), unless there was toxicity. If the toxicity was attributable to one component alone, then this component was to be withdrawn and the other components continued until progression. Eg, if oxaliplatin was discontinued due to toxicity, 5-FU and leucovorin (or equivalent folinic acid preparation) were to be continued until progression along with the blinded study medication. Patients were permitted to continue first-line chemotherapy and blinded study medication after progression if, in the opinion of the investigator, this would be beneficial.

Statistical methods

The primary analysis of PFS was to be performed after 850 PFS events had occurred. An interim analysis of OS was performed at the time of the primary analysis of PFS, and a final OS analysis is planned to be performed after 950 deaths have occurred.

PFS was defined as the time from randomisation to the earlier date of objective progression or death. Patients who were still alive at the time of the analysis, without a progression event, were to be censored at the date of their last evaluable objective tumour assessment. PFS events occurring after the start of subsequent cancer treatment or after 2 or more missing/NE RECIST assessments were censored. PFS was analysed using a log rank test stratified by PS (0 or 1), baseline albumin (<4 and ≥4 g/dL) and baseline ALP (≤160 and >160 U/L), in accordance with the stratification used at randomisation. The effect of treatment was estimated by the adjusted HR together with its 2-sided 95% confidence interval (CI), which was to be calculated from a Cox proportional hazards model fitting for the same covariates defined in an identical manner to the log rank test. The protocolled hurdle to achieve superiority was $p<0.05$ (which would be a $HR<0.87$ based on 850 events) and to achieve non inferiority the upper limit of the 95% CI needed to be less than 1.2.

Non-inferiority

The criteria to demonstrate non-inferiority was an upper 2 sided 95% confidence limit for the PFS HR of less than 1.2. Based on the protocolled event rate, this criterion required that the point estimate was 1.05 or less.

Sensitivity analysis

The primary analysis used tumour measurements and assessments provided on the eCRFs. To assess the sensitivity of the primary analysis, a supportive analysis was performed, which used the tumour assessments data provided by an independent central review. This analysis used the same methodology and model as the primary analysis.

Impact of the adaptive design

All patients randomised to either the cediranib 20 mg or bevacizumab 5mg/kg arms were included in the final PFS analysis. Application of methodology described by Todd and Stallard in combination with the prospectively defined dose selection criteria applied by the IDMC, revealed the dose selection criteria more than compensated for any inflation of the Type-1 error in the study and therefore, an adjustment of the Type-1 error for the primary analysis is not considered necessary.

Subgroup analysis

The consistency of the treatment effect for PFS were assessed across several subgroups and a global interaction test was used to verify the overall strength of evidence for consistency.

Secondary variables

The interim analysis of OS used the same methodology and model as described for PFS. Response rate was analysed using logistic regression, adjusting for the same set of covariates as PFS. The effect of treatment was estimated using the adjusted odds ratio and its 95% CI together with the response rate in each treatment group. The analysis of time to worsening of QoL and time to worsening of disease related symptoms used the same methodology as described for PFS. Type-1 error was controlled within each of these distinct families of secondary endpoints, but not between them, by testing variables using a closed hierarchical testing procedure.

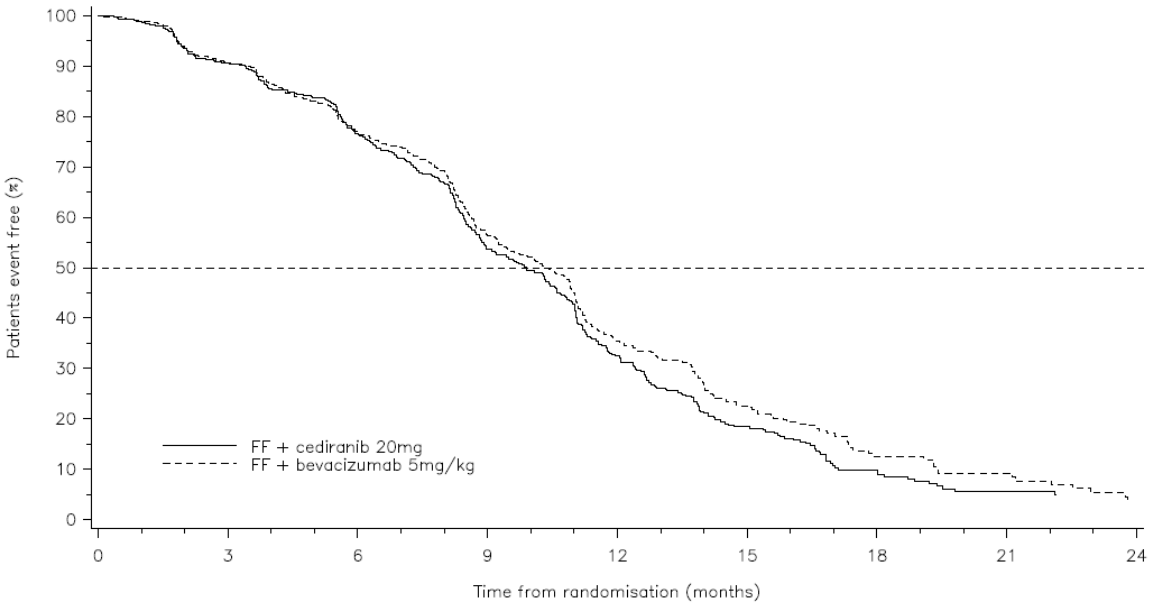
Subject population

In total, 1805 patients from 206 centres in 28 countries were enrolled into this study. A total of 226 randomised patients across the 3 treatment arms (cediranib 20 mg: 74; cediranib 30 mg:76; bevacizumab: 76) contributed to the end-of-Phase II analysis. Of the 709 patients randomised to cediranib 20 mg arm, 705 received active cediranib. In the bevacizumab arm, of the 713 patients randomised, 704 received active bevacizumab. In total, 791 patients were ongoing in the study at the time of data cut-off (15th November 2009), although the majority (579) had completed both randomised treatment and treatment with FOLFOX. Demographic and baseline characteristics indicate that the study population was representative of the intended population.

Summary of efficacy results

In the ITT population, 471 (66.4%) patients in the cediranib 20 mg arm and 453 (63.5%) patients in the bevacizumab arm had progressions that were included in the primary analysis of PFS. The rate of disease progression was numerically higher in patients receiving cediranib 20 mg compared with patients receiving bevacizumab (HR: 1.10 [95% CI: 0.97, 1.25]; p=0.1190). Although the difference between treatment groups was not statistically significant, the pre-defined non-inferiority criteria, which required the upper 95% confidence limit to be <1.2, was not met. The estimated median PFS for patients randomised to cediranib 20 mg compared to bevacizumab was 9.9 months and 10.3 months, respectively. The Kaplan-Meier plot is presented in Figure S1.

Figure S1 Kaplan-Meier figure of progression-free survival (Full Analysis Set, ITT)



Number of patients at risk*

MONTH	000	003	006	009	012	015	018	021	024
FF + cediranib 20mg	709	591	454	296	132	059	022	010	007
FF + bevacizumab 5mg/kg	713	601	472	319	140	064	022	012	004

* The number of patients at risk denotes the number of patients event free at the beginning of the period.

The results from all sensitivity analyses on PFS were consistent with the primary analysis with the HR estimate (1.04–1.12) being numerically in favour of bevacizumab. In addition, the global interaction test was not significant and each subgroup investigated had a HR within the range of values included by the 95% CI for the primary PFS analysis. Therefore, of the prospectively defined subgroups assessed there was no subgroup where the relative effect of cediranib to bevacizumab differed.

The results of the interim statistical analysis of OS for the ITT population (cediranib 20 mg vs bevacizumab) revealed the treatment arms were similar (HR: 0.94 [95% CI: 0.79, 1.12]; p=0.5459). The median OS in the cediranib 20 mg arm was 22.8 months, compared with 21.3 months in the bevacizumab arm.

Objective tumour response (ORR), defined as patients with a confirmed[1] response of "complete response (CR)" or "partial response (PR)" was similar between the 2 treatment arms (cediranib 20 mg: ORR 328 [46.3%], CR 12 [1.7%]; bevacizumab: ORR 337 [47.3%], CR 11 [1.5%]).

[1] Confirmed responses were responses of PR or CR, confirmed by a subsequent PR or CR at least 28 days later by a subsequent evaluable assessment. Intervening assessments of NE or SD were allowable as long as the initial RECIST response was confirmed.

The mean reduction in tumour size at first RECIST assessment was 23.2% in the cediranib 20 mg arm and 22.1% in the bevacizumab arm. The mean best reduction in tumour size was 40.0% in the cediranib 20 mg arm and 38.8% in the bevacizumab arm. Among responders, duration of response was numerically longer on the bevacizumab arm compared to the cediranib 20 mg arm (median 9.6 months compared to 8.6 months).

Summary of safety results

The median number of cycles of 5-FU was 12.0 in the cediranib 20 mg arm and 14.0 in the bevacizumab arm. For each treatment arm, the median number of complete mFOLFOX6 cycles was comparable to the median number of oxaliplatin cycles (cediranib 20 mg: 10.0, bevacizumab: 12.0).

As summarised in Figure S1, there was no difference in PFS curves between the 2 treatment arms during the first 6 months of treatment, thus this is a relevant period to look at chemotherapy dose intensity as there is no confounding due to a difference in efficacy. A near 'complete' complement of chemotherapy over this period would be 12 or 13 cycles. During the first 6 months of treatment , more patients in the bevacizumab arm compared with the cediranib 20 mg arm received ≥12 cycles of 5-FU (50.7% vs 35.2%) and oxaliplatin (42.8% vs 27.2%).

The number of patients who had at least 1 AE in any category during the course of the study is presented in Table S2. Overall, the incidence of Grade 3 or more AEs and SAEs was higher in the cediranib arm and there was a slightly higher incidence of AEs leading to discontinuation in the cediranib arm. The incidence of AEs with outcome of death was similar in both arms.

Table S2 Number of patients who had at least 1 AE in each category (Safety set)

	Number (%) of patients[a]	
	Cediranib 20 mg (N=709)	**Bevacizumab (N=704)**
Any AE	701 (99.4)	693 (98.4)
Any AE of CTCAE grade 3 or higher	546 (77.4)	494 (70.2)
Any AE with an outcome of death[b]	19 (2.7)	23 (3.3)
Any SAE (including AEs with an outcome of death)[b]	275 (39.0)	231 (32.8)
Any SAE with outcome other than death[c]	268 (38.0)	220 (31.3)
Any AE leading to discontinuation of treatment with cediranib/placebo	168 (23.8)	147 (20.9)
Any AE leading to discontinuation of treatment with bevacizumab/placebo	163 (23.1)	147 (20.9)

a Patients with multiple AEs in the same category were counted only once in that category. Patients with events in >1 category were counted once in each of those categories.
b Death occurred up to and including 30 days post last day of dosing.
c All patients who had a SAE with a non-fatal outcome (regardless of whether they later had a fatal SAE).
CTCAE version 3.0 used.

The most common AEs in the cediranib 20 mg arm were diarrhoea (493 [69.9%]), nausea (359 [50.9%]), fatigue (317 [45.0%]), neutropenia (306 [43.4%]) and hypertension (296 [42.0%]).

Diarrhoea was the most frequent AE in both treatment arms (cediranib 20 mg: 493 [69.9%], bevacizumab: 357 [50.7%]). The frequency of diarrhoea, neutropenia, hypertension, stomatitis, thrombocytopenia, abdominal pain, dysphonia and palmar-plantar erythrodysesthesia syndrome (PPE) was >5% higher in the cediranib 20 mg arm compared to the bevacizumab arm. Conversely, the frequency of constipation was >5% higher in the bevacizumab arm compared to the cediranib 20 mg arm.

The frequency of Grade ≥3 diarrhoea was >5% higher in the cediranib 20mg arm compared to the bevacizumab arm (97 [13.8%] vs 41 [5.8%]). There was also a noticeable difference in Grade 2 events (cediranib 20 mg: 193 [27.4%], bevacizumab: 128 [18.2%]).Overall there was a higher frequency of dose pauses due to diarrhoea in the cediranib 20 mg arm compared to the bevacizumab arm (10% vs 3%, respectively).

The frequency of Grade≥3 neutropenia was also >5% higher in the cediranib 20 mg arm compared to the bevacizumab arm (224 [31.8%] vs 166 [23.6%]). The largest difference between the 2 treatment arms was seen in the frequency of Grade 3 events (cediranib 20 mg: 145 [20.6%]; bevacizumab: 99 [14.1%]). Although this resulted in more dose delays in the cediranib 20 mg arm, it did not lead to clinically important consequences such as febrile nuetropenia or hospitalisation.

The number of deaths during treatment and within 30 days of last dose of IP was similar between treatment arms (cediranib 20 mg: 39 [5.5%], bevacizumab: 42 [6.0%]). From these, deaths due to disease progression/worsening only (cediranib 20 mg: 20 [2.8%], bevacizumab: 20 [2.8%]) and AEs with outcome of death only (cediranib 20 mg: 18 [2.6%], bevacizumab: 20 [2.8%]) were the most common reasons for death during this period.

Overall, when assessing AE's by important medical topics (based on the emerging safety profile of cediranib and the labels of bevacizumab and other small molecule TKIs), the 2 treatment arms were similar and reflected the known profile of VEGF signalling inhibition in combination with chemotherapy.

Overall, the clinical laboratory findings and vital signs were consistent with the known toxicity profiles of cediranib, bevacizumab and for mFOLFOX6-related abnormalities, together with the advanced disease under investigation and pre-existing medical conditions. The findings for ECG were unremarkable with no differences between treatment arms.

Summary of Health related quality of life results

The PRO results revealed statistically significant differences between treatment arms in favour of bevacizumab in all of the PRO endpoints which appeared to reflect differences in the tolerability profile, particularly diarrhoea, rather than any differential effect on efficacy.

Patients receiving cediranib 30 mg

In total, 192 patients received cediranib 30 mg+ mFOLFOX6. The AE profile of the cediranib 30 mg arm was generally comparable to the cediranib 20 mg arm in terms of the types of AEs reported, though cediranib 30 mg had a higher incidence of SAEs (90 [46.9%]) and DAEs (60 [31.3%]) compared to the cediranib 20mg arm. The most common AEs on cediranib 30 mg were: diarrhoea (78.1%), nausea (52.1%), hypertension (49.5%) and fatigue (49.0%).