AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00051
Edition Number	1
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A Randomised, Double-blind, Phase III Study to Compare the Efficacy and Safety of Cediranib (AZD2171) when added to 5-fluorouracil, Leucovorin and Oxaliplatin (FOLFOX) or Capecitabine and Oxaliplatin (XELOX) with the Efficacy and Safety of Placebo when added to FOLFOX or XELOX in Patients with Previously Untreated Metastatic Colorectal Cancer

Study dates: First patient enrolled: 3 November 2006
Last patient enrolled: 20 August 2008

Phase of development: Therapeutic confirmatory (III)

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

Study centres

Patients were enrolled at 112 centres in: Argentina, Australia, Brazil, Bulgaria, China, Czech Republic, Germany, Hungary, India, Korea, Philippines, Poland, Switzerland, Taiwan, UK.

Publications

Hoff et al. Ann Oncol 21 (suppl 8) page viii9. October 2010. Abstract LBA19.

Objectives

Table S1 Primary and secondary objectives and associated outcome variables

Objectives	Variables
Primary	
To determine the efficacy of cediranib when added to FOLFOX or XELOX compared with the efficacy of FOLFOX or XELOX alone in patients with previously untreated metastatic colorectal cancer (CRC).	Co-primary variables: progression-free survival (PFS) and overall survival (OS).
Secondary	
To determine the efficacy of cediranib when added to FOLFOX or XELOX compared with the efficacy of FOLFOX or XELOX alone in patients with previously untreated metastatic CRC.	Assessment of overall response rate (complete response + partial response) and duration of response.
To determine the rate of resection of liver metastases in patients with previously untreated metastatic CRC receiving cediranib when added to FOLFOX or XELOX compared with patients receiving FOLFOX or XELOX alone.	Rate of resection of liver metastases.
To determine the incidence of wound healing complications in patients with previously untreated metastatic CRC receiving cediranib when added to FOLFOX or XELOX compared to patients receiving FOLFOX or XELOX alone.	Incidence of wound healing complications.
To determine the safety and tolerability of cediranib when added to FOLFOX or XELOX compared to the safety and tolerability of FOLFOX or XELOX alone.	AEs, laboratory findings (clinical chemistry, haematology, urinalysis), vital signs, physical examination, WHO performance status, ECG.

Study design

Randomised, double-blind, parallel-group, placebo-controlled study to compare efficacy and safety of cediranib + chemotherapy (investigator choice of FOLFOX4, mFOLFOX6, or XELOX) vs the chemotherapy alone in patients with previously untreated metastatic CRC.

Patients were initially randomised 1:1:1 (cediranib 20 mg: cediranib 30 mg: placebo), plus chemotherapy. Two doses of cediranib were included at study start to determine the most appropriate dose for efficacy and safety, but it was planned that one dose would be selected for continuation after the HORIZON programme dose decision/end-of-Phase II analysis. An external Independent Data Monitoring Committee (IDMC) considered criteria relating to efficacy that were pre-defined by AstraZeneca, in addition to monitoring safety. The IDMC advised that cediranib 20 mg met the efficacy criteria, and this dose was selected by AstraZeneca for continuation. The IDMC endorsed this decision but did not disclose the

results. After dropping the 30 mg arm, the randomisation schedule changed to 2:1 (cediranib 20 mg: placebo). Patients who had been randomised to cediranib 30 mg were unblinded and given the option to continue with open-label study treatment (either continue with 30 mg or reduce to 20 mg). There was a formal interim analysis of efficacy once 50% of the target number of OS events had been reached.

Target patient population and sample size

Males and females aged ≥18 years with histologically or cytologically confirmed Stage IV (metastatic) CRC who had received no prior systemic therapy for metastatic disease; WHO performance status (PS) 0-1; measurable disease according to RECIST. Any adjuvant/ neoadjuvant oxaliplatin to have been received >12 months before study entry and adjuvant/ neoadjuvant 5-FU to have been received >6 months before study entry. Patients who had previously been disease-free following neoadjuvant chemotherapy and resection of all primary tumour and metastatic disease were eligible. Prior therapy with VEGF signalling inhibitors was not allowed.

In total, approximately 1050 patients were planned to be randomised to the initial 3 treatment arms. Following discontinuation of the 30 mg arm, patients were randomised only to the cediranib 20 mg or placebo arms, with no effect on overall study size.

Administration of investigational product, comparator and chemotherapy

Cediranib: To maintain the blind, patients received either 1 x 30 mg tablet + placebo matching cediranib 20 mg, or 1 x 20 mg tablet + placebo matching cediranib 30 mg. After the 30 mg arm was dropped, the double-dummy design was no longer necessary. Cediranib and placebo tablets were taken orally once daily, no less than 1 h before, or more than 2 h after a meal. Dose reductions were permitted for management of toxicity. Batch numbers for cediranib and placebo tablets are provided in the main study report.

FOLFOX4: oxaliplatin 85 mg/m^2 2 h iv infusion on Day 1; leucovorin 200 mg/m^2 2 h iv infusion on Days 1 and 2; 5-FU 400 mg/m^2 iv bolus (immediately after completion of oxaliplatin/leucovorin infusions on Days 1 and 2, respectively), followed immediately by 5-FU 600 mg/m^2 22 h continuous iv infusion on Days 1 and 2. **mFOLFOX6:** oxaliplatin 85 mg/m^2 2 h iv infusion on Day 1; leucovorin 400 mg/m^2 2 h iv infusion on Day 1; 5-FU 400 mg/m^2 iv bolus (immediately after completion of oxaliplatin/leucovorin infusions on Day 1), followed immediately by 5-FU 2400 mg/m^2 46 h continuous iv infusion. **XELOX:** oxaliplatin 130 mg/m^2 2 h iv infusion on Day 1; capecitabine 1000 mg/m^2 orally twice daily on Days 1 to 14. Cycles repeated every 2 weeks (FOLFOX regimens) or every 3 weeks (XELOX) until disease progression (or other discontinuation criteria met (unless there was toxicity. If toxicity was due to 1 component alone, this component was to be withdrawn and the other components continued until progression.

Duration of blinded treatment

Patients could continue with blinded study treatment after disease progression following discussion with AstraZeneca, if in the opinion of the investigator the patient was receiving

benefit, until toxicity or withdrawal of consent. There was no crossover to active cediranib for patients on placebo. Patients with disease progression who continued with blinded treatment were also to be offered an effective 2nd-line treatment (VEGF inhibitors not permitted).

Statistical methods

The final analysis of co-primary and secondary variables was to be performed when approximately 510 OS events had occurred within the 2 continued treatment arms. For each variable, the comparison of interest was cediranib 20 mg + chemotherapy vs placebo + chemotherapy. There were no comparisons to assess the effect of chemotherapy on either co-primary variable, as choice of chemotherapy was not randomised. No adjustment to the final α level due to discontinuing the 30 mg arm was required, since application of pre-defined decision criteria during the dose decision/end-of Phase II analysis more than offset any need for adjustment. Efficacy data for cediranib 30 mg were not summarised or subjected to statistical analysis as the blind was broken for these patients at the dose decision point.

The co-primary variables OS and PFS were analysed separately using a log-rank test stratified by performance status, type of chemotherapy, liver function and study phase (ie, patients who were/were not included in the HORIZON programme dose decision/EOPII analysis). To preserve the overall Type I error on the co-primary variables, PFS was tested first and if that was significant, OS was tested. The significance level for the co-primary endpoints was adjusted to account for the formal interim analysis once the actual number of events became known. When this was done, $p<0.04993$ was significant for PFS, and $p<0.04909$ was significant for OS. The primary analysis was based on investigator site assessment of progression (RECIST), censoring patients who progressed or died after ≥2 consecutive non-evaluable visits or started another anti-cancer therapy prior to progression. Supportive analyses were undertaken using an interval censored approach, alternative censoring mechanisms and independent central review of scans. In addition, subgroup analyses were undertaken for WHO PS, type of chemotherapy, baseline liver function, study phase, baseline LDH, baseline VEGF, age, sex, treatment in China or East Asia vs rest of world, prior adjuvant therapy, liver only metastases at baseline. A global interaction test was performed to test the overall strength of evidence for consistency over all these subgroups.

Patient population

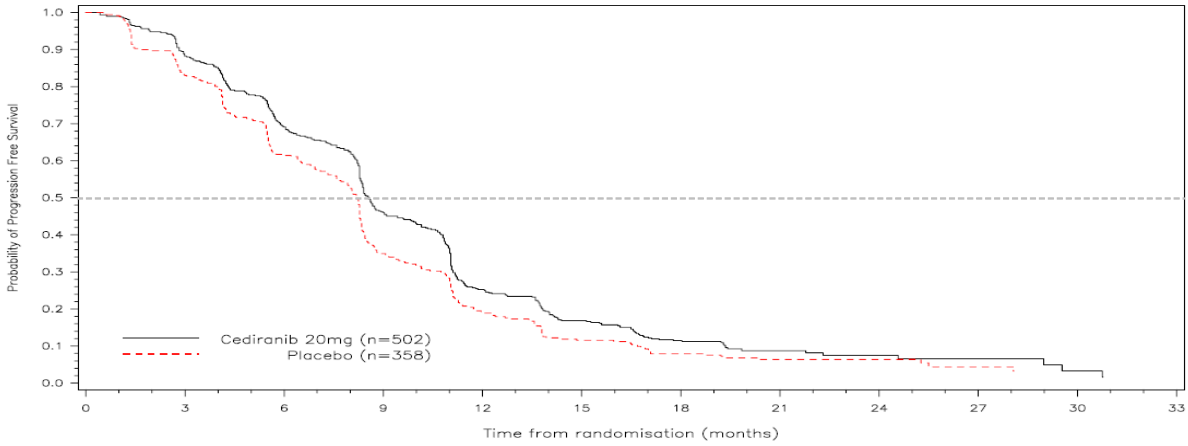
1254 patients were enrolled, of which 1076 were randomised: 502 to cediranib 20 mg, 358 to placebo, and 216 to cediranib 30 mg. Median age of the patients was 58 years (range: 22 to 83 years); 59.4% were male, 66.7% were Caucasian, 29.5% were Oriental. At baseline, 57.8% had WHO PS 0 and 42.2% had PS 1; 60.5% had colon cancer and 39.5% had rectal cancer. Demographic and baseline characteristics were generally well balanced across the arms and the study population was representative of the intended population. The number of important deviations was low. Only 1 patient (in the placebo arm) was unblinded prior to progression, no patients received the wrong study treatment, and only 2 randomised patients (both in cediranib 20 mg arm) received no study medication.

Summary of efficacy results

By the time of data cut-off (21 March 2010), 440 (87.6%) patients in the cediranib 20 mg arm and 326 (91.1%) in the placebo arm had a PFS event, with 412 and 308 progression events included in the primary analysis. 523 (60.8% of the study population) patients had died by data cut-off; median follow-up was 21.8 months on cediranib 20 mg, and 23.1 months on placebo. There was a statistically significant improvement in PFS for the cediranib 20 mg compared with placebo (HR=0.84, 95% CI 0.72, 0.98, p=0.0121), with separation between the Kaplan-Meier curves from the time of first scan and throughout the course of the study. However, the magnitude of the PFS benefit was relatively small. There was no difference in OS for cediranib 20 mg compared with placebo (HR=0.94 95% CI 0.79, 1.12, p=0.5707). Median OS was 19.7 months (cediranib 20 mg) and 18.9 months (placebo).

Sensitivity analyses were consistent with the results of the co-primary analyses, indicating that censoring methods and investigator vs central review of scans did not affect the conclusions. PFS and OS outcomes were generally consistent across subgroups. Baseline WHO PS 0 indicated a differential effect from WHO PS1, with the benefit for cediranib being in favour of PS 0; however, the pre-defined global interaction test was not significant.

Figure S1 Kaplan-Meier plot of PFS (Full Analysis Set, ITT)



Number of patients at risk*

Month	000	003	006	009	012	015	018	021	024	027	030	033
Cediranib 20mg	502	411	311	204	111	074	047	016	009	006	002	001
Placebo	358	283	203	111	060	035	023	013	009	004	001	000

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

To control for multiplicity, the secondary variables were tested using the following hierarchy: response rate, rate of resection of liver metastases, and duration of response. There were no statistically significant differences between treatment arms for the secondary efficacy endpoints. Response rate was 50.6% on the cediranib 20 mg arm and 49.7% on the placebo arm. Median best change from baseline in tumour size was -42.43% on the cediranib arm, and -41.65% on placebo. The proportion of patients with liver metastases at baseline who underwent liver resection was similar between arms: 5.4% on cediranib and 6.3% on placebo.

There were no statistical/analytical issues or bias that would compromise interpretation of the results. The placebo arm behaved as expected from previous studies.

Summary of safety results

500 patients received cediranib 20 mg, 358 received placebo. During the first 12 months of treatment, median dose intensity for cediranib and placebo was 100% in each 3-month period, though mean and 1st quartile dose intensities were lower in the cediranib arm than on placebo. Mean daily dose of cediranib/placebo was 18.6 mg for the cediranib 20 mg arm, and 19.3 mg for the placebo arm. Greater than 70% of patients in both arms were treated to progression at least with randomised treatment, and 81 (16.1%) patients on cediranib 20 mg and 69 (19.3%) on placebo continued on blinded study treatment for ≥1 month post-progression.

The median number of cycles of chemotherapy where all constituents were administered was lower in the cediranib 20 mg arm than the placebo arm: FOLFOX4: 9 cycles vs 11 cycles; mFOLFOX6: 10 cycles vs 11 cycles; XELOX: 6 cycles vs 7 cycles. Patients on the cediranib 20 mg arm received a lower median dose intensity of chemotherapy than those on placebo. Median dose intensity in the first 6 months for the fluoropyrimidine component (ie, 5-FU/ capecitabine) and oxaliplatin was approximately 7% to 9% lower on the cediranib arm compared with the placebo arm. The proportion of patients treated to progression with randomised treatment and the fluoropyrimidine component of the chemotherapy was 41.6% on cediranib vs 57.7% on placebo.

Table S2 Number of patients with at least 1 AE in any category (Safety set)

Category of AE	Number (%) of patients [a]	
	Cediranib 20 mg (N=500)	Placebo (N=358)
Any adverse event	495 (99.0)	353 (98.6)
Any adverse event of CTCAE grade 3 or higher	389 (77.8)	222 (62.0)
SAEs (including events with outcome of death)	204 (40.8)	105 (29.3)
Adverse events with outcome of death [b]	14 (2.8)	12 (3.4)
SAEs with outcome other than death [c]	200 (40.0)	99 (27.7)
AEs leading to permanent discontinuation of cediranib/placebo (DAEs)	114 (22.8)	58 (16.2)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in >1 category are counted once in each of those categories.
b AEs starting on treatment and up to and including 30 days post last day of dosing.
c All patients experiencing an SAE with non-fatal outcome (regardless if they later had a fatal SAE)

The incidence of grade ≥3 AEs, SAEs, and AEs requiring dose pause, reduction, or discontinuation of randomised study treatment was higher on cediranib 20 mg than placebo.

Most common AEs: diarrhoea (71.0%), nausea (51.4%), vomiting (46.6%), and hypertension (46.0%) on cediranib 20 mg; and diarrhoea (48.0%), nausea (47.2%), and vomiting (36.6%) on placebo. Most common AEs ≥grade 3 were more frequent on cediranib 20 mg than

placebo: diarrhoea (21.2% vs 8.1%), neutropenia (15.8% vs 10.6%), thrombocytopenia (12.6% vs 7.0%), hypertension (11.0% vs 2.0%), fatigue (7.6% vs 3.1%).

289 (57.8%) patients in the cediranib 20 mg arm, and 234 (65.4%) in the placebo arm died; the majority of deaths in both arms were due to disease progression/worsening. The most commonly reported AE with outcome of death was pneumonia: 3 patients (0.6%) on cediranib 20 mg vs 2 (0.6%) on placebo. Most common SAE in either arm was diarrhoea: 6.8% on cediranib 20 mg vs 3.1% on placebo. Diarrhoea was also the most common DAE: 3.0% on cediranib 20 mg vs 0.8% on placebo.

The haematology, clinical chemistry, and vital signs results were consistent with the known toxicity profiles of cediranib, bevacizumab, and the chemotherapy regimens given. The incidence of wound healing complications on cediranib 20 mg was comparable to placebo.

The safety profile of cediranib 20 mg was generally consistent with previous studies. Acknowledging that caution is required when making comparisons between the chemotherapy regimens, as chemotherapy was not randomised, the AE profiles across the 3 regimens was generally consistent, although the AE profile for FOLFOX4 appeared more favourable than would be expected from historical data.

214 patients received cediranib 30 mg. The AE profile of the cediranib 30 mg arm was generally comparable to the 20 mg arm in terms of the types of AEs reported, though cediranib 30 mg had a higher incidence of reports of AEs with outcome of death 19 (8.9%) patients and discontinuations due to AEs 79 (36.9%) patients. The most common AEs on cediranib 30 mg were: diarrhoea (70.6%), hypertension (47.2%), and nausea (44.4%).