Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00039
Edition Number	1
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A Two Part Study in Japanese Patients with Previously Untreated Metastatic Colorectal Cancer, Consisting of an Open-label Phase I Part to assess the Safety and Tolerability of cediranib (AZD2171) in combination with 5 fluorouracil, Leucovorin and Oxaliplatin (FOLFOX) followed by a Phase II, Randomised, Double-blind, Parallel Group Study to Assess the Efficacy of cediranib (AZD2171) in combination with FOLFOX, compared to FOLFOX alone

Study dates: First patient enrolled: 12 June 2007
Last patient enrolled: 22 January 2009

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

Three centres in Japan in Part A (Phase I part), 29 centres in Japan in Part B (Phase II part).

Publications

None at the time of writing this report.

Objectives and associated outcome variables for Part A

Objectives	Variables
Primary objective	**Primary variables**
To assess the safety and tolerability of AZD2171 (cediranib) in combination with mFOLFOX6 (5 fluorouracil (5-FU), Leucovorin and Oxaliplatin) in patients with previously untreated metastatic CRC.	Adverse events, vital signs, body weight, clinical chemistry, haematology, urinalysis, WHO performance status, ECG and physical examination
Secondary objectives	**Secondary variables**
To determine the steady-state PK of cediranib when given in combination with mFOLFOX6	cediranib steady-state PK parameters ($C_{ss,max}$, $C_{ss,min}$, t_{max}, AUC_{ss})
To determine the PK of oxaliplatin and 5-FU in combination with repeated doses of cediranib	5-FU PK parameter (C_{max}), Oxaliplatin PK parameters (C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, CL, $t_{1/2\lambda z}$, MRT)
Exploratory objective	**Exploratory variables**
To explore the efficacy of cediranib in combination with mFOLFOX6 in patients with previously untreated metastatic CRC as measured by RECIST and change in tumour size.	ORR (CR+PR), Changes in tumour size

Note: Results regarding pharmacogenetic analysis of the activity of cediranib will be reported separately.

Objectives and associated outcome variables for Part B

Objectives	Variables
Primary objective	**Primary variables**
To assess the efficacy of cediranib in combination with mFOLFOX6 compared to the efficacy of mFOLFOX6 alone in patients with previously untreated metastatic CRC by assessment of progression free survival (PFS).	PFS
Secondary objectives	**Secondary variables**
The efficacy of cediranib in combination with mFOLFOX6 compared to the efficacy of mFOLFOX6 alone in patients with previously untreated metastatic CRC by assessment of objective response rate (ORR: complete response [CR] + partial response [PR]), change in tumour size and overall survival (OS).	ORR (CR+PR), Changes in tumour size, OS
The safety and tolerability of cediranib in combination with mFOLFOX6.	Adverse events, clinical chemistry, haematology, urinalysis, vital signs, physical examinations, body weight, WHO performance status, ECG
Exploratory objective	**Exploratory variables**
To investigate the relationship between the effect of cediranib in combination with mFOLFOX6 on biomarkers in serum and plasma in optional blood samples.	VEGF, sVEGFR2

Objectives	Variables
To investigate the relationship between biomarkers in serum and plasma and the clinical efficacy of cediranib in combination with mFOLFOX6 in optional blood samples.	VEGF, sVEGFR2

Note: Results regarding biomarkers in optional archival tumour samples and pharmacogenetic analysis of the activity of cediranib will be reported separately.

Study design

This was a two part study in Japanese patients with previously untreated metastatic colorectal cancer, consisting of an open-label phase I part to assess the safety and tolerability of cediranib in combination with FOLFOX followed by a phase II, randomised, double-blind, parallel group study to assess the efficacy of cediranib in combination with FOLFOX, compared to FOLFOX alone. The patients did not enter the both parts.

Part A (phase I part)

This was an open-label phase I part to assess the safety and tolerability of cediranib in combination with mFOLFOX6 in Japanese patients at doses that had already been confirmed to be sufficiently tolerated in Western patients.

A cohort of patients was recruited to receive cediranib 20 mg + mFOLFOX6. Once the safety of cediranib 20 mg + mFOLFOX6 had been confirmed, a second cohort was recruited to receive cediranib 30 mg + mFOLFOX6. A safety review committee assessed safety and tolerability of each dose once 3 evaluable patients within a dose cohort had completed 28 days of continuous daily dosing. Based on the number of intolerant toxicity observed, additional patients might be recruited to each dose cohort to further assess the safety. Part B started after the safety and tolerability of both doses had been confirmed by the safety review committee.

Part B (phase II part)

This was a Phase II, randomised, double-blind, parallel group study to assess the efficacy of cediranib in combination with mFOLFOX6, compared to mFOLFOX6 alone.

Patients were randomised to receive either once daily cediranib 20 mg + mFOLFOX6 or cediranib 30 mg + mFOLFOX6 or cediranib placebo + mFOLFOX6 in a 1:1:1 ratio. Patients were stratified at randomisation according to a two-level liver function covariate (based on baseline albumin and alkaline phosphatase [ALP]) and World Health Organisation (WHO) performance status (0 vs 1).

Target subject population and sample size

Patients must be aged 18 years and over. Patients must have histologically- or cytologically-confirmed metastatic CRC; patients must not have received prior systemic therapy for metastatic disease and must have completed any adjuvant/neoadjuvant oxaliplatin therapy at least 12 months before study entry (5-FU adjuvant/neoadjuvant therapy can have been received at least 6 months prior to study entry). Patients must have a WHO performance

status of 0 or 1 and must have measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (in Part A, it was not necessarily required).

Investigational product: dosage, mode of administration

The doses of cediranib or matching placebo to be used in this study were made up from the available tablet strengths 15 mg, 20 mg and 30 mg. Cediranib or placebo was orally administered once daily.

Combination chemotherapy: dosage, mode of administration

Chemotherapy medications (mFOLFOX6) were standard treatments for patients entered into the study, and repeated every two weeks (1 cycle).

Duration of treatment

Treatment was to continue for an indefinite period of time until objective disease progression, occurrence of toxicity, death, withdrawal of patient consent or other discontinuation criterion was met.

Statistical methods

All data were presented descriptively. The number of patients required in Part A was based on the desire to gain adequate safety information on the combination whilst exposing as few subjects as possible to the study medication and procedures (a minimum of 3 evaluable patients is required for assessment by the safety review committee).

The formal analysis of this study was performed when approximately 105 progression events were observed across the 3 groups in Part B.

There were two comparisons of interest, cediranib 30 mg + FOLFOX vs FOLFOX alone and cediranib 20 mg + FOLFOX vs FOLFOX alone. A total number of 165 patients (55 patients per arm) were required in Part B to have 80% power to detect true hazard ratios of 0.6 with one-sided 10% level, assuming median PFS of 9 months for FOLFOX alone, an accrual period of 18 months for Part B and minimum follow up period of 12 months.

As the primary analysis for PFS, a log rank test stratified by WHO performance status (0 or 1) and a two-level baseline liver function covariate were used for each comparison. A two-sided alpha 0.2 was used for each comparison. The effect of treatment was estimated by the adjusted HR together with its 95% confidence interval, which was calculated from a Cox proportional hazards model fitting for the same covariates defined in an identical manner to the log rank test. PFS was summarised by treatment group using Kaplan Meier method.

Results for Part A

Patient population (Part A)

In total 13 Japanese patients were enrolled into Part A (cediranib 20 mg cohort: 6, cediranib 30 mg cohort: 7) and received the study treatment. Patients were representative of the target population (previously untreated metastatic colorectal cancer).

Summary of pharmacokinetic results (Part A)

Geometric means of $C_{ss\ max}$ and $C_{ss\ min}$ were 52.9 ng/mL and 20.4 ng/mL for cediranib 20 mg, and 105 ng/mL and 44.8 ng/mL for cediranib 30 mg, respectively. Geometric means of AUC_{ss} were 762 ng·hr/mL for cediranib 20 mg and 1590 ng·hr/mL for cediranib 30 mg. t_{max} (median) was 3.0 hours and 3.2 hours for cediranib 20 mg and 30 mg, respectively.

Summary of safety results (Part A)

SAEs were observed in 2 of 6 patients in the cediranib 20 mg cohort and 3 of 7 patients in the cediranib 30 mg cohort, but there were no fatal AEs in either cohort during the study. For AEs leading to discontinuation of cediranib there were 3 and 2 patients in the cediranib 20 mg, and cediranib 30 mg cohorts, respectively. The numbers of patients with CTCAE grade 3 or higher were 5 in each cohort. The Safety profile and tolerability of cediranib 20 mg and 30 mg in combination with FOLFOX was judged acceptable to transfer to Part B.

Results for Part B

Patient population (Part B)

In total, 172 patients were randomised into three treatment groups, 58 into the FOLFOX + cediranib 20 mg, 56 into the FOLFOX + cediranib 30 mg and 58 into the FOLFOX + placebo. Patients were representative of the target population (previously untreated metastatic colorectal cancer). Baseline characteristics of patients were generally balanced between the three treatment cohorts.

Summary of efficacy results (Part B)

The hazard ratio of FOLFOX + cediranib 20 mg to FOLFOX + placebo was 0.70 (95% CI: 0.44-1.11, p=0.1665). The PFS effect of FOLFOX + cediranib 20 mg group met the pre-defined criteria of two-sided $p<0.2$ (ie. one-sided $p<0.1$). The hazard ratio of the FOLFOX + cediranib 30 mg group to the FOLFOX + placebo group was 0.82 (95% CI: 0.52-1.131, p=0.2605) which did not meet the criteria of $p<0.2$. Median PFS was 10.23 months for the FOLFOX + cediranib 20 mg group, 8.85 months for the FOLFOX + cediranib 30 mg group and 8.32 months for FOLFOX + placebo group.

There were 31 (53.4%), 39 (69.6%) and 31 (53.4%) patients who experienced a confirmed objective response of either a complete response or a partial response in the FOLFOX + cediranib 20 mg, FOLFOX + cediranib 30 mg and FOLFOX + placebo groups, respectively.

Median duration of response was 9.2, 6.7 and 7.1 months for the FOLFOX + cediranib 20 mg, FOLFOX + cediranib 30 mg and FOLFOX + placebo groups, respectively.

Summary of pharmacodynamic results (Part B)

Median levels of VEGF increased on treatment with cediranib in a dose dependent manner. Mean sVEGFR2 levels decreased dose- and time-dependently on treatment with cediranib.

Summary of safety results (Part B)

Actual median durations of exposure to cediranib/placebo were 241.5 days, 213.0 days and 223.5 days in the FOLFOX + cediranib 20 mg, FOLFOX + cediranib 30 mg and FOLFOX + placebo groups, respectively. During the first 3 months treatment, the mean % dose intensity of cediranib/placebo was lower in the FOLFOX + cediranib 30 mg group at 72.4% compared to the FOLFOX + cediranib 20 mg and FOLFOX + placebo groups (85.9% and 93.1%, respectively). Likewise, the mean % dose intensity of chemotherapy was lower in the FOLFOX + cediranib 30 mg group at 64.6%, 68.8% and 64.2% for 5-FU, leucovorin and oxaliplatin, respectively, compared to the FOLFOX + cediranib 20 mg (72.1%, 76.8% and 71.3%, respectively) and FOLFOX + placebo groups (81.4%, 83.8% and 82.5%, respectively).

AEs were reported in all patients for all treatment groups. The proportion of patients with SAEs was 39.7%, 39.3% and 19.0% in the FOLFOX + cediranib 20 mg, FOLFOX + cediranib 30 mg and FOLFOX + placebo groups, respectively. There were no fatal AEs during the study. For AEs leading to discontinuation of cediranib/placebo there were 19.0% and 26.8% patients in the FOLFOX + cediranib 20 mg and FOLFOX + cediranib 30 mg groups, respectively.

Table S 1 Number (%) of patients with AE in any category (Part B): Safety Set

AE category	Number (%) of patients[a]					
	FOLFOX + cediranib 20 mg n=58		FOLFOX + cediranib 30 mg n=56		FOLFOX + Placebo n=58	
Any AE	**58**	**(100.0)**	**56**	**(100.0)**	**58**	**(100.0)**
Any cediranib causally[b] related AE	57	(98.3)	56	(100.0)	50	(86.2)
Any chemotherapy causally[b] related AE	58	(100.0)	56	(100.0)	58	(100.0)
Any AE of CTC grade 3 or higher	**38**	**(65.5)**	**42**	**(75.0)**	**21**	**(36.2)**
Any cediranib causally[b] related AE of CTC grade 3 or higher	29	(50.0)	38	(67.9)	12	(20.7)
Any chemotherapy causally[b] related AE of CTC grade 3 or higher	35	(60.3)	38	(67.9)	18	(31.0)
Any AE with outcome = death[e]	**0**		**0**		**0**	
Any SAE (including events with outcome = death)	**23**	**(39.7)**	**22**	**(39.3)**	**11**	**(19.0)**
Any SAE with outcome other than death[c]	**23**	**(39.7)**	**22**	**(39.3)**	**11**	**(19.0)**
Any cediranib causally[b] related SAE with outcome other than death	16	(27.6)	20	(35.7)	5	(8.6)
Any chemotherapy causally[b] related SAE with outcome other than death	19	(32.8)	18	(32.1)	7	(12.1)
Any AE leading to discontinuation of treatment with cediranib/Placebo	**11**	**(19.0)**	**15**	**(26.8)**	**0**	
Any cediranib causally[b] related AE leading to discontinuation of treatment with cediranib/Placebo	10	(17.2)	14	(25.0)	0	
Any chemotherapy causally[b] related AE leading to discontinuation of treatment with cediranib/Placebo	8	(13.8)	9	(16.1)	0	
Any other significant AE[d]	**32**	**(55.2)**	**35**	**(62.5)**	**9**	**(15.5)**

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] Causally related to IP as assessed by the Investigator
[c] All patients experiencing an SAE with non-fatal outcome (regardless if they later had a fatal SAE)
[d] Any AE, other than those reported as SAEs or led to discontinuation of treatment or led to temporarily stopping treatment or dose reduction with IP deemed by the sponsor to be significant. These findings have been derived from a subjective assessment of AE data
[e] Death occurred up to and including 30 days post last day of dosing
CTCAE version 3.0 used

The most frequently reported AEs in the FOLFOX + cediranib 20 mg and FOLFOX + cediranib 30 mg groups were diarrhoea (91.4% and 87.5%, respectively) and hypertension (81.0% and 85.7%, respectively) of which the severity was mostly CTCAE grade 1 or 2. The frequency of these AEs was higher in the cediranib groups compared to the FOLFOX + placebo group (diarrhoea: 37.9%, hypertension: 31.0%). AEs leading to discontinuation except for decreased appetite, diarrhoea and pneumonia were isolated in the FOLFOX + cediranib 20 mg and FOLFOX + cediranib 30 mg groups. There were no patients who had an AE leading to discontinuation of placebo in the FOLFOX + placebo group.

Date of the report

15 September 2010