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A Phase I, Open-label, Non-randomized Study, to assess the Safety and Tolerability of Cediranib (AZD2171) in combination with Cisplatin plus a Fluropyrimidine (Capecitabine or S-1) in Japanese Patients with Previously Untreated Locally Advanced or Metastatic Unresectable Gastric Cancer

Study dates: First subject enrolled: 5 August 2009
                                    Last subject enrolled: 7 December 2009
Phase of development: Clinical exploratory (I)

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

Four centres in Japan

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**
To assess the safety and tolerability in combination with capecitabine/cisplatin or S-1/cisplatin in Japanese patients with previously untreated locally advanced or metastatic unresectable gastric cancer	Adverse events, clinical laboratory, vital signs, body weight, ECG, WHO performance status, physical examination
Secondary	**Secondary**
To determine the steady-state pharmacokinetics (PK) of cediranib alone and in combination with capecitabine/cisplatin or S-1/cisplatin in Japanese patients	Cediranib steady-state PK parameters ($C_{ss,max}$, $C_{ss,min}$, AUC_{ss}, AUC_{0-8}, t_{max})
To examine the effects of cediranib on the PK of capecitabine and cisplatin in Japanese patients	Cisplatin, S-1 and capecitabine PK parameters (C_{max}, AUC_{0-t}, AUC, CL, $t_{1/2\lambda z}$, MRT, t_{max})
Exploratory	
To obtain the preliminary efficacy of cediranib in combination with capecitabine/cisplatin or S-1/cisplatin in Japanese patients with previously untreated locally advanced or metastatic unresectable GC as measured by tumour response according to RECIST criteria and change in tumour size in patients with measurable lesions.	Tumour response, changes in tumour size

C_{max}: Maximum plasma drug concentration after single dose administration, $C_{ss,max}$: Maximum concentration at steady state, $C_{ss,min}$: Minimum concentration at steady state, t_{max}: Time to maximum concentration, AUC: Area under plasma concentration-time curve, AUC_{ss}: Area under plasma concentration-time curve during any dosing interval at steady state, AUC_{0-t} : Area under plasma concentration-time curve from time 0 to t, CL: Total body clearance of drug from plasma, AUC_{0-8}: Area under plasma concentration-time curve from 0 to 8 hr, $t_{1/2\lambda z}$: Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve, MRT : Mean residence time

Study design

This was an open label, non-randomised, multicenter, phase I study to assess the safety and tolerability of cediranib in combination with capecitabine/cisplatin or S-1/cisplatin in Japanese patients with previously untreated locally advanced or metastatic unresectable gastric cancer.

Patients were entered initially in the S-1/cisplatin treatment group. After completion of the enrolment, patients were entered in the capecitabine/cisplatin treatment group.

Target subject population

Male and female Japanese patients aged 20 years or over with histological or cytological confirmation of previously untreated locally advanced or metastatic unresectable gastric adenocarcinoma including the gastric cardia and esophagogastric junction. Patients must have no prior systemic therapy for locally advanced or metastatic gastric cancer. Patients must have a World Health Organisation (WHO) performance status of 0 or 1.

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

Patients were to receive cediranib in combination with S-1/cisplatin or capecitabine /cisplatin.

Cediranib

The tablet strength of cediranib was 15 mg and 20 mg. Cediranib was orally administered once daily.

Combination chemotherapy

In the cediranib + S-1 + cisplatin cohort, S-1 was given orally at a dose of 40-60 mg according to the patient's body surface for 3 weeks followed by a 2-week rest period, and cisplatin was given intravenously at a dose of 60 mg/m^2 over 2 hours followed by a 5-week rest period.

In the cediranib + capecitabine + cisplatin cohort, capecitabine was given orally at a dose of 1000 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period, and cisplatin was given intravenously at a dose of 80 mg/m^2 over 2 hours followed by a 3-week rest period.

Duration of treatment

Study 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 met.

Statistical methods and sample size

Safety, pharmacokinetics and efficacy data were presented descriptively. No formal hypothesis testing was performed. The number of patients, 6 to 9 for each cohort, was based on the desire to gain adequate safety and pharmacokinetic information on the combination whilst exposing as few subjects as possible to the study medication and procedures.

Subject population

In total 16 Japanese patients were enrolled into this study, and 14 received the study treatment (6 in the cediranib + S-1 + cisplatin cohort and 8 in the cediranib + capecitabine + cisplatin cohort). The median age was 60.5 years, and 5 of the 14 patients were 65 years or more. Male patients accounted for 64.3% (9/14 patients). The patients were representative of the target population (previously untreated advanced unresectable gastric cancer).

Summary of efficacy results

There was one patient with the best tumour overall objective response of partial response in the cediranib + S-1 + cisplatin cohort, and 4 patients with stable disease (2 in each cohort)

Summary of pharmacokinetic results

Cediranib: Comparing the data within each patient, the PK parameters for cediranib in the presence of S-1+cisplatin or capecitabine+cisplatin were similar to the PK parameters for cediranib when administered alone; however limited data were available, particularly for the S-1 arm (N=2; N=4 for the capecitabine arm).

S-1: Comparing the data within each patient, the PK parameters for S-1 (5-FU) in combination with both cediranib+cisplatin were similar to the PK parameters for S-1 (5-FU) when administered with cisplatin alone; however insufficient data were available to draw meaningful conclusions (N=2).

Capecitabine: Four patients had capecitabine (5-FU) data available both in combination with both cediranib+cisplatin and cisplatin alone, however only 2 of those received the same dose of capecitabine on both occasions (the comparison for patients where the dose differed was done on dose normalised data, assuming dose linearity across the dose range studied). One out of 4 patients had a higher 5-FU exposure in the presence of cediranib (C_{max} = 983 ng/mL; AUC_{0-4} = 889 ng.h/mL) than in the absence of cediranib (C_{max} = 132 ng/mL; AUC_{0-4} = 187 ng.h/mL), which was also higher than the exposure observed in any other patients in either the S-1 or capecitabine treatment arms. The reason for this is not clear. Comparing the data within each patient for the other 3 patients, the PK parameters for capecitabine (5-FU) in combination with both cediranib+cisplatin were similar to the PK parameters for capecitabine (5-FU) when administered with cisplatin alone.

Cisplatin (total platinum equivalents): Two patients in the S-1 arm and 4 patients in the capecitabine arm had cisplatin data (total platinum equivalents) available both in the presence of cediranib+S-1/capecitabine and S-1/capecitabine alone. For all patients, the cisplatin (total platinum equivalents) exposure showed a slight increase on the day when cediranib+S-1/capecitabine was administered compared to the day when cisplatin was administered with TS-1/capecitabine alone. However this may be due to accumulation of platinum as a result of the prolonged terminal plasma half-life of platinum (samples collected in the absence of cediranib were collected following single dose cisplatin whereas those collected in the presence of cediranib were collected following multiple dose cisplatin).

Summary of safety results

All patients treated with the study medication experienced AE during the course of the study. DLTs were identified in one patient each of both cohorts; decreased appetite in the cediranib + S-1 + cisplatin cohort, and anorexia (decreased appetite), and fatigue and hyponatremia in the cediranib + capecitabine + cisplatin regimen. SAEs were reported in 3 of the 6 patients in the cediranib + S-1 + cisplatin regimen (decrease appetite, decreased appetite/hyponatremia/ stomatitis, and syncope), and 2 of the 8 patients in the cediranib + capecitabine + cisplatin

regimen (decreased appetite/ hyponatremia/fatigue, and pulmonary embolism) but there were no fatal AEs in either cohort. For AEs leading to discontinuation of cediranib there were 2 and 1 patients in the cediranib + S-1 + cisplatin and cediranib + capecitabine + cisplatin cohorts, respectively. The numbers of patients with CTCAE grade 3 or higher were 4 and 6 in the cediranib + S-1 + cisplatin and cediranib + capecitabine + cisplatin cohorts, respectively.

The number of patients who had at least 1 AE in any category during the course of the study is presented in Table S2.

Table S2   **Summary of number (%) of patients who had at least 1 AE in any category: Safety Set**

AE category	Number (%) patients[a]		
	Cediranib + S-1 + Cisplatin	Cediranib + Capecitabine + Cisplatin	Total
	n=6	n=8	n=14
Any AE	6 (100.0)	8 (100.0)	14 (100.0)
Any AE of CTC grade 3 or higher	5 (83.3)	6 (75.0)	11 (78.6)
Any AE with outcome = death[d]	0	0	0
Any SAE (including events with outcome = death)	3 (50.0)	2 (25.0)	5 (35.7)
Any SAE with outcome other than death[b]	3 (50.0)	2 (25.0)	5 (35.7)
Any AE leading to discontinuation of treatment with cediranib	2 (33.3)	1 (12.5)	3 (21.4)
Any other significant AE[c]	0	0	0

[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] All patients experiencing an SAE with non-fatal outcome (regardless if they later had a fatal SAE)

[c] Any AE, other than those reported as SAEs or led to discontinuation of treatment, or led to temporarily stopping treatment or dose reduction with cediranib, deemed by the sponsor to be significant. These findings have been derived from a subjective assessment of AE data

[d] Death occurred up to and including 30 days post last day of dosing

CTCAE version 3 used

Data derived from Table 11.3.2.1.

Date of the report

29 September 2010