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ORIGINAL ARTICLE

Phase I study of cediranib in combination with cisplatin plus fluoropyrimidine (S-1 or capecitabine) in Japanese patients with previously untreated advanced gastric cancer

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Abstract
Purpose The primary objective of this Phase I study was to assess the safety and tolerability of the vascular endothelial growth factor signalling inhibitor cediranib in combination with cisplatin plus an oral fluoropyrimidine, in Japanese patients with previously untreated advanced gastric cancer.
Methods Patients received continuous, once-daily oral doses of cediranib 20 mg in combination with either cisplatin (60 mg/m^2 iv day 1) plus S-1 (40–60 mg bid, days 1–21) every 5 weeks for a maximum of eight cycles [Arm A]; or cisplatin (80 mg/m^2 iv, day 1) plus capecitabine (1,000 mg/m^2 bid, days 1–14) every 3 weeks for a maximum of six cycles [Arm B]. In both arms, the assessment period for dose-limiting toxicities (DLTs) was the first 21 days of cycle 1.
Results Fourteen patients (Arm A, $n = 6$; Arm B, $n = 8$) were enrolled and received at least one dose of cediranib. One patient in each arm experienced a DLT (Arm A; decreased appetite, grade 3; Arm B, decreased appetite, fatigue and hyponatraemia, all grade 3). Overall, the most common adverse events were decreased appetite, fatigue and nausea (all $n = 13$ [92.9%]). Preliminary efficacy evaluation showed one confirmed (Arm A) and three unconfirmed (Arm A, $n = 1$; Arm B, $n = 2$) partial responses that were ongoing at data cut-off.
Conclusions Cediranib 20 mg/day in combination with cisplatin and S-1 or capecitabine was tolerable, with no new toxicities identified, and showed preliminary evidence of antitumour activity.

Keywords Cediranib · VEGF signalling · Phase I · Gastric cancer · Japanese

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Introduction

Gastric cancer is the most common malignancy in Japan. GLOBOCAN figures revealed that in 2008, there were 102,040 new cases of gastric cancer, and 50,156 deaths were attributed to this disease in Japan [1]. The only curative treatment is surgery, however, over half of patients present with inoperable tumours. For those patients with unresectable tumours and receiving best supportive care, outcomes are extremely poor with median survival times ranging from 3 to 5 months [2–4].

Combination chemotherapy regimens with platinum-based cisplatin plus an oral fluoropyrimidine are commonly used as first-line treatment for advanced gastric cancer in Japan [5]. This treatment regimen is based on early-phase clinical trials that showed cisplatin in combination with 5-fluorouracil (5-FU) or oral fluoropyrimidines yielded overall response rates of approximately 40% and median survival times of 7–13 months [6–10].

Vascular endothelial growth factor (VEGF) plays an essential role in the formation and maintenance of tumour vasculature [11]. The addition of bevacizumab, an anti-VEGF-A antibody, to standard chemotherapy has demonstrated clinical benefit in patients with advanced colorectal cancer [12–14] and non-small-cell lung cancer [15].

Cediranib is an oral, highly potent VEGF signalling inhibitor with activity against all three VEGF receptors [16, 17]. Initial clinical evaluation of cediranib monotherapy demonstrated that it is suitable for once-daily oral dosing in Japanese [18] and Western [19] patients, with biological activity at doses ≥20 mg/day [19]. Subsequent Phase I studies showed that cediranib 30 mg/day was generally well tolerated in combination with various standard anticancer treatments, with encouraging preliminary evidence of antitumour activity [20–23]. However, when the protocol for the present study was being developed, emerging data from Phase II and III trials indicated that cediranib 20 mg was the highest tolerable dose suitable for chronic once-daily dosing in combination with chemotherapy, with higher doses not considered to be more effective [24, 25]. Consequently, the dose of cediranib selected for this combination study was 20 mg/day. The primary objective of the current Phase I study (ClinicalTrials.gov, number NCT00960349) was to assess the safety and tolerability of cediranib 20 mg/day in combination with capecitabine/cisplatin or S-1/cisplatin in Japanese patients with previously untreated advanced gastric cancer.

Methods

Patients

Japanese patients ≥20 years of age with histologically or cytologically confirmed previously untreated recurrent or metastatic unresectable gastric adenocarcinoma were eligible for inclusion. Patients were required to have a life expectancy ≥12 weeks and a World Health Organization performance status of 0 or 1. The main exclusion criteria were as follows: significant respiratory, cardiac, hepatic or renal dysfunction; unstable brain metastases; poorly controlled hypertension; significant haemorrhage (>30 ml bleeding/episode in the previous 3 months) or haemoptysis (>5 ml fresh blood in the previous 4 weeks); arterial thromboembolic events in the previous 12 months; history of other malignancies within the previous 5 years; any unresolved toxicity according to Common Terminology Criteria for Adverse Events (CTCAE) from prior radiotherapy; recent (<14 days) major thoracic or abdominal surgery; and incomplete recovery from prior surgery. All patients provided written informed consent. The study was approved by the institutional review board at each participating centre and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on Bioethics [26].

Study design

This was a multicentre, open-label, non-randomized, Phase I study. Eligible patients received cediranib 20 mg/day orally (starting on day 2 in cycle 1) in combination with either cisplatin (60 mg/m^2 intravenous [iv], day 1) plus S-1 (40–60 mg orally twice daily, days 1–21) [Arm A] or cisplatin (80 mg/m^2 iv, day 1) plus capecitabine (1,000 mg/m^2 orally twice daily, days 1–14) [Arm B] (Fig. 1). One cycle of treatment in Arm A was 5 weeks, and one cycle of treatment in Arm B was 3 weeks. The rest periods in Arms A (2 weeks) and B (1 week) were consistent with standard clinical practice for administration of S-1 and capecitabine, respectively. The chemotherapy treatments in Arms A and B were continued for a maximum of eight and six cycles, respectively. Thereafter, treatment of cediranib plus S-1/capecitabine could be continued until a discontinuation criterion was met. Patients were initially entered into Arm A. Following enrolment of six patients into Arm A, patients were then entered into Arm B.

The primary study objective was to assess the safety and tolerability of cediranib in combination with S-1/cisplatin or capecitabine/cisplatin. After entry of six evaluable patients in each arm, a safety review committee (SRC) discussed whether the regimen was tolerated. The treatment was considered tolerable if ≤1 of the six patients experienced a DLT. If 2–3 of the six patients experienced a DLT, either the SRC recommended the combination was tolerated or the cohort was expanded to include three further evaluable patients. If ≥4 patients experienced a DLT, the treatment was considered intolerable.

In both arms, a DLT was any toxicity considered related to study drug that commenced within the first 21 days of cycle 1 and met any of the following criteria: hypertension or diarrhoea that required cessation of cediranib treatment; an absolute neutrophil count <500/mm^3 for ≥5 days despite growth factor support; a platelet count <50,000/mm^3 for ≥5 days; a dose delay to starting any chemotherapy agent in cycle 2 for longer than 14 days; dose reductions of cediranib due to cediranib-related toxicity; a single increase from baseline in the QT interval corrected for heart rate

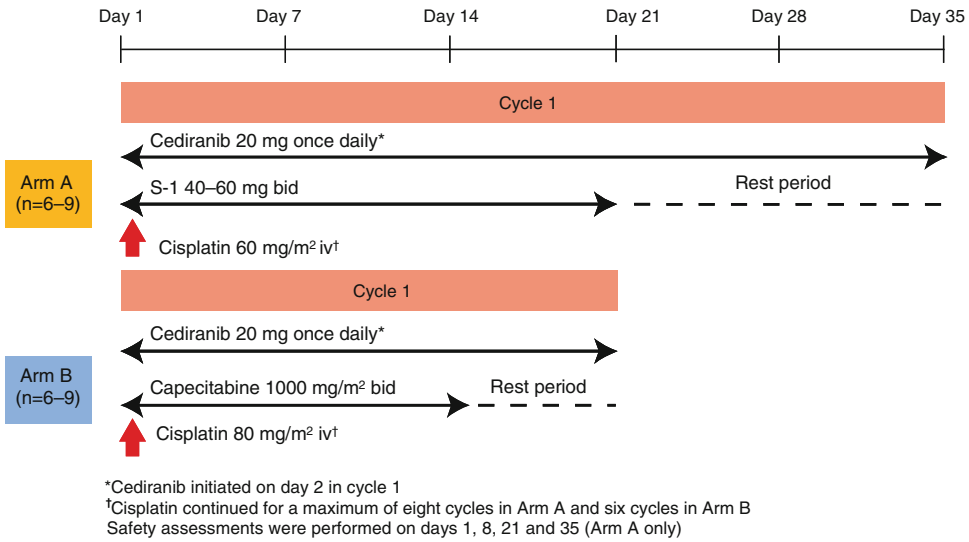

Fig. 1 Study design

(QTc) of 60 ms that results in a QTc of at least 460 ms; two QTc measurements >490 ms taken at least 24 h apart; and any other CTCAE grade ≥3 that was, in the opinion of the investigator and the SRC, not clearly related to disease progression, clinically significant and related to the study drug.

Secondary objectives were to determine the steady-state pharmacokinetics (PK) of cediranib alone and in combination with chemotherapy and to investigate the potential effect of cediranib on the PK of the chemotherapy components (cisplatin and S-1/capecitabine [5-FU]). An exploratory objective was to assess the preliminary efficacy of the combination regimens by measurement of tumour response according to the Response Evaluation Criteria In Solid Tumours (RECIST version 1.0) [27].

Assessment of safety and tolerability

After a full physical examination at enrolment, toxicity was monitored throughout the study by the assessment of adverse events (AEs), which were graded according to CTCAE version 3.0. Vital signs (blood pressure [BP], pulse rate and body temperature) were measured, electrocardiograms recorded and samples taken for clinical chemistry, haematology assessment and urinalysis at the screening visit and on days 1, 8 and 21 in both arms; patients in Arm A repeated these assessments on day 35.

Pharmacokinetic assessment

To evaluate steady-state cediranib PK, blood samples were taken immediately before and 1, 2, 4, 6, 8 and 24 h after cediranib treatment on the final day of cycle 1 (cediranib alone) and day 1 of cycle 2 (presence of chemotherapy). To evaluate S-1/capecitabine (5-FU) PK, blood samples were collected immediately before and 0.5, 1, 2, 4, 6 and 8 h after S-1/capecitabine treatment on day 1 of cycle 1 (absence of cediranib) and day 1 of cycle 2 (presence of cediranib). To evaluate cisplatin PK, blood samples were taken pre-dose; 5 min before the end of the 2-h iv infusion; and 2.5, 3, 4, 6, 8 and 24 h post start of infusion on day 1 of cycle 1 (absence of cediranib) and day 1 of cycle 2 (presence of cediranib).

Plasma concentrations of cediranib, capecitabine (5-FU only), S-1 (5-FU only) and cisplatin (total platinum equivalents) were determined using high-performance liquid chromatography with mass spectrometry (LC–MS/MS). PK parameters were calculated using standard non-compartmental analysis.

Assessment of tumour response

Objective tumour assessments determined by RECIST were performed every 12 weeks from the start of treatment until disease progression, death or discontinuation of cediranib due to any other reason.

Results

Patient characteristics

Between August and December 2009, 14 patients were recruited into Arm A ($n = 6$) or Arm B ($n = 8$). Patient demographic and baseline characteristics are summarized in Table 1. At data cut-off (4 January 2010), three patients in Arm A and five patients in Arm B were still receiving cediranib, and one patient in Arm B continued to receive capecitabine and cisplatin. The reasons for discontinuation of cediranib treatment were clinical disease progression

Table 1 Patient demographics and baseline characteristics

Characteristics	Cediranib + S-1 + cisplatin ($n = 6$)	Cediranib + capecitabine + cisplatin ($n = 8$)	Total ($n = 14$)
Age, years			
Median	59.5	60.5	60.5
Range	53–71	27–72	27–72
Sex, *n* (%)			
Male	4 (66.7)	5 (62.5)	9 (64.3)
Female	2 (33.3)	3 (37.5)	5 (35.7)
WHO performance status, *n* (%)			
0	3 (50.0)	4 (50.0)	7 (50.0)
1	3 (50.0)	4 (50.0)	7 (50.0)
Number of metastatic sites (%)			
1	1 (16.7)	0	1 (7.1)
>1	5 (83.3)	8 (100.0)	13 (92.9)
Recurrence, *n* (%)	0	1 (12.5)	1 (7.1)
Stage IV, *n* (%)	6 (100)	7 (87.5)	13 (92.9)
Measurable target lesion, *n* (%)	5 (83.3)	6 (75.0)	11 (78.6)
Histology, *n* (%)			
Adenocarcinoma (intestinal)	1 (16.7)	3 (37.5)	4 (28.6)
Adenocarcinoma (diffuse)	1 (16.7)	0	1 (7.1)
Tubular adenocarcinoma	3 (50.0)	2 (25.0)	5 (35.7)
Signet ring carcinoma	1 (16.7)	3 (37.5)	4 (28.6)

WHO World Health Organization

(Arms A and B, $n = 1$), AEs (Arms A and B, $n = 1$) and withdrawal of consent (Arm A, $n = 1$). One patient in Arm B was revealed ineligible at cycle 2 due to a pulmonary embolism at baseline; this patient discontinued study treatment but was included in safety analyses.

Safety and tolerability

All patients received at least one dose of cediranib and were therefore evaluable for safety. The median (range) daily cediranib dose was 16.0 (12.9–20.0) mg in Arm A and 15.9 (13.7–20.0) mg in Arm B, and median (range) duration of actual exposure to cediranib was 72.5 days (13–127) for Arm A and 38.5 days (13–62) for Arm B. The median (range) number of chemotherapy cycles received was 2.5 (1–4) for both arms.

Overall, 12 (86%) [Arm A, $n = 5$; Arm B, $n = 7$] patients experienced one or more cediranib dose interruptions, with one patient from each arm having a dose reduction to 15 mg/day. All six patients in Arm A experienced a dose reduction or interruption of S-1 and seven patients (87.5%) in Arm B experienced a dose reduction or interruption of capecitabine. Five patients in each arm (Arm A, 83.3%; Arm B, 62.5%) had a dose reduction or dose delay of cisplatin. Two patients in Arm A (alopecia, $n = 1$; diarrhoea, stomatitis, fatigue, decreased appetite and hyponatraemia, $n = 1$) and one patient in Arm B (diarrhoea, fatigue, decreased appetite and hypomagnesaemia) experienced AEs that led to permanent discontinuation of cediranib treatment.

Table 2 Most common adverse events (incidence > 30% in total population)

AE, preferred term	All grades, *n* (%)		
	Cediranib + S-1 + cisplatin ($n = 6$)	Cediranib + capecitabine + cisplatin ($n = 8$)	Total ($n = 14$)
Decreased appetite	5	8	13 (92.9)
Fatigue	5	8	13 (92.9)
Nausea	5	8	13 (92.9)
Constipation	3	7	10 (71.4)
Diarrhoea	5	5	10 (71.4)
Stomatitis	4	6	10 (71.4)
Hypertension	3	6	9 (64.3)
Weight decreased	5	4	9 (64.3)
Neutropenia	5	3	8 (57.1)
Vomiting	3	5	8 (57.1)
Alopecia	2	4	6 (42.9)
Dysphonia	2	4	6 (42.9)
Hiccups	1	4	5 (35.7)
Leukopenia	3	2	5 (35.7)
Proteinuria	3	2	5 (35.7)

AE adverse event

DLTs were reported in one patient in Arm A (decreased appetite, grade 3) and one patient in Arm B (decreased appetite, fatigue and hyponatraemia; all grade 3). In Arm A, the investigator assessed that decreased appetite was related to S-1 and/or cisplatin. In Arm B, the investigator judged decreased appetite and hyponatraemia related to cediranib, S-1 and cisplatin, and stomatitis related to cediranib and S-1. The SRC decided neither DLT warranted cohort expansion for further evaluation of safety.

The most commonly reported AEs were decreased appetite, fatigue and nausea (all $n = 13$ [92.9%]) [Table 2]. Five (83%) patients in Arm A and six (75%) patients in Arm B experienced AEs grade ≥3 (Table 3). Hypertension was reported as an AE in nine patients (Arm A, $n = 3$; Arm B, $n = 6$), only one (Arm B) of which was

Table 3 Any CTCAE grade ≥3 adverse events

	Grade	Cediranib + S-1 + cisplatin ($n = 6$)	Cediranib + capecitabine + cisplatin ($n = 8$)	Total ($n = 14$)
Neutropenia	3	3	2	5 (35.7)
Hypokalaemia	3	0	3	3 (21.4)
Hyponatraemia	3	1	2	3 (21.4)
Decreased appetite	3	1	1	2 (14.3)
Fatigue	3	0	2	2 (14.3)
Anaemia	3	0	1	1 (7.1)
Diarrhoea	3	1	0	1 (7.1)
Haemoglobin decreased	3	1	0	1 (7.1)
Hyperbilirubinaemia	3	0	1	1 (7.1)
Hyperglycaemia	3	0	1	1 (7.1)
Hypertension	3	0	1	1 (7.1)
Hypomagnesaemia	3	0	1	1 (7.1)
Platelet count decreased	3	1	0	1 (7.1)
Pulmonary embolism	4	0	1	1 (7.1)
Stomatitis	3	1	0	1 (7.1)
Syncope	4	1	0	1 (7.1)
White blood cell count decreased	3	1	0	1 (7.1)
Wound infection	3	1	0	1 (7.1)

grade 3; no action was taken regarding dose adjustment. One patient in Arm A experienced grade 4 transient syncope on day 6, cycle 2. A head computed tomography (CT) scan showed no cerebral haemorrhage and the syncope resolved on the same day it appeared. The investigator considered this event to be related to cediranib, S-1 and cisplatin. One patient from Arm B experienced a grade 4 pulmonary embolism that was identified on day 18, cycle 2 after the patient complained of chest pain. After careful review of the baseline CT scan, the pulmonary embolism was found to be pre-existing at study entry. The investigator judged the event as worsening of the pulmonary embolism related to cediranib, capecitabine and cisplatin. Increases in thyroid stimulating hormone were observed in both arms, but free T4 and T3 remained within normal limits for the majority of these patients. Increases were observed in alanine aminotransferase and aspartate aminotransferase in both arms, but most values were generally within the normal ranges. There were no clinically relevant results related to electrocardiogram, physical findings or other safety observations.

Five serious AEs (SAEs) were reported in three patients in Arm A (decreased appetite, $n = 2$; hyponatraemia, $n = 1$; stomatitis, $n = 1$; syncope, $n = 1$), and in addition to the pulmonary embolism in one patient, three other SAEs were reported in a separate patient in Arm B (decreased appetite, hyponatraemia and fatigue). All SAEs, except for the pulmonary embolism, had resolved by data cut-off. There were no deaths in the period to data cut-off in either arm.

Pharmacokinetics

A summary of PK parameters for cediranib, cisplatin and S-1/capecitabine is shown in Table 4. Only six patients (Arm A, $n = 2$; Arm B, $n = 4$) were evaluable for PK analysis, having completed the planned sampling schedule; therefore, limited data were available for within-patient comparison. In Arm A ($n = 2$), the PK parameters for S-1 in combination with both cediranib and cisplatin were similar to those for S-1 when administered with cisplatin alone, and the PK parameters for cediranib were similar in the presence and absence of chemotherapy; however, there were insufficient data to draw meaningful conclusions on the PK in Arm A. Based on limited data from Arm B ($n = 4$), the cediranib PK parameters were similar in the absence and presence of capecitabine/cisplatin. The PK profile of capecitabine was generally similar in the absence and presence of cediranib; one patient (patient 4 in Table 4) had a higher exposure in the presence of cediranib, but the reason for this is not clear as no interaction would be expected. In all patients (Arms A and B), slight increases in exposure to cisplatin (total platinum equivalents; maximum plasma concentration [C_{max}] and area under plasma concentration–time curve from time zero to 8 h [AUC_{0-8h}]) were observed when cediranib was administered with chemotherapy compared with chemotherapy alone; however, samples collected in the absence of cediranib were obtained following single-dose cisplatin, whereas those collected in the presence of cediranib were obtained following multiple-dose cisplatin.

Efficacy

Seven patients (Arm A, $n = 4$; Arm B, $n = 3$) had a post-baseline scan and were therefore evaluable for efficacy. Tumour shrinkage was observed in five of these patients (Fig. 2); the mean largest change from baseline was −41.8% in Arm A ($n = 4$) and −26.3% in Arm B ($n = 3$). One patient in Arm A had a partial response that was ongoing at data cut-off (duration >79 days). Among the four patients with stable disease ($n = 2$ in each arm), three had unconfirmed partial responses at data cut-off. One patient in each arm had a best response of progressive disease.

Table 4 Summary of pharmacokinetic parameters

Analyte	Patient	Combination	C_{max}, ng/ml	AUC, ng h/ml
Arm A				
Cediranib	Patient 1	Cediranib alone	25.5	378
		Cediranib + S-1 + cisplatin	51.3	598
	Patient 2	Cediranib alone	153	2,640
		Cediranib + S-1 + cisplatin	192	2,780
5-FU	Patient 1 (60 mg S-1)	S-1 + cisplatin	58.6	302
		Cediranib + S-1 + cisplatin	92.1	446
	Patient 2 (50 mg S-1)	S-1 + cisplatin	182	908
		Cediranib + S-1 + cisplatin	130	644
Cisplatin	Patient 1	S-1 + cisplatin	2,740	12,700
		Cediranib + S-1 + cisplatin	3,040	14,100
	Patient 2	S-1 + cisplatin	2,400	10,400
		Cediranib + S-1 + cisplatin	2,790	12,600
Arm B				
Cediranib	All patients ($n = 4$)	Cediranib alone	77.5 (32.9–99.9)	1,180 (479–1,800)
	All patients ($n = 4$)	Cediranib + capecitabine + cisplatin	86.3 (50.2–115)	1,220 (687–1,850)
5-FU	Patient 3 (1,600 mg capecitabine)	Capecitabine + cisplatin	130	283
		Cediranib + capecitabine + cisplatin	284	421
	Patient 4 (1,750 mg capecitabine)	Capecitabine + cisplatin	132	187
		Cediranib + capecitabine + cisplatin	983	889
	Patient 5 (1,450 mg capecitabine)	Capecitabine + cisplatin	167	305
		Cediranib + capecitabine + cisplatin	105[a]	335[a]
	Patient 6 (1,600 mg capecitabine)	Capecitabine + cisplatin	287	518
		Cediranib + capecitabine + cisplatin	392[b]	647[b]
Cisplatin	All patients ($n = 4$)	Capecitabine + cisplatin	3,430 (2,720–3,840)	16,900 (13,500–18,900)
	All patients ($n = 4$)	Cediranib + capecitabine + cisplatin	4,620 (3,230–5,720)	21,700 (16,600–23,600)

AUC_{0-24h} was calculated for cediranib; AUC_{0-4h} for capecitabine (5-FU); and AUC_{0-8h} for cisplatin and S-1 (5-FU)

In Arm B, cediranib and cisplatin parameters are expressed as mean (min–max); all other data are individual patient values as there are insufficient data to summarize by mean value

AUC area under the plasma concentration–time curve, C_{max} maximum plasma (peak) drug concentration

[a] Dose of 1,300 mg capecitabine administered: data dose normalized to 1,450 mg

[b] Dose of 1,200 mg capecitabine administered: data dose normalized to 1,600 mg

Discussion

The impact of conventional chemotherapy on advanced gastric cancer remains modest, with median survival times reaching a plateau of 7–13 months [6–8]. More effective treatment options are needed. In this Phase I study, we evaluated the VEGF signalling inhibitor cediranib in combination with cisplatin and S-1 or capecitabine in Japanese patients with previously untreated locally advanced or metastatic unresectable gastric adenocarcinoma. Treatment was tolerable, with only one patient in each arm experiencing a DLT. Overall, the safety profile of each regimen was consistent with previous studies of the individual agents in patients with advanced cancer [8, 9, 18, 19, 23, 28–30], and no new toxicities were identified. The most commonly reported AEs were decreased appetite, fatigue and nausea. There were no reports of severe hypertension as a SAE, and the overall incidence of hypertension was consistent with that reported in a Phase I study of cediranib monotherapy in Japanese patients [18].

Insufficient PK data preclude any meaningful conclusions relating to Arm A. Based on the limited PK data from Arm B, there was no clear indication of a consistent interaction between cediranib and cisplatin/capecitabine. This is not unexpected as it is considered unlikely that cisplatin, capecitabine or S-1 would affect cediranib routes of metabolism [31]. The slight increases in cisplatin exposure observed in all patients when cediranib was administered with chemotherapy compared to chemotherapy alone may be due to an accumulation of platinum following multiple dosing.

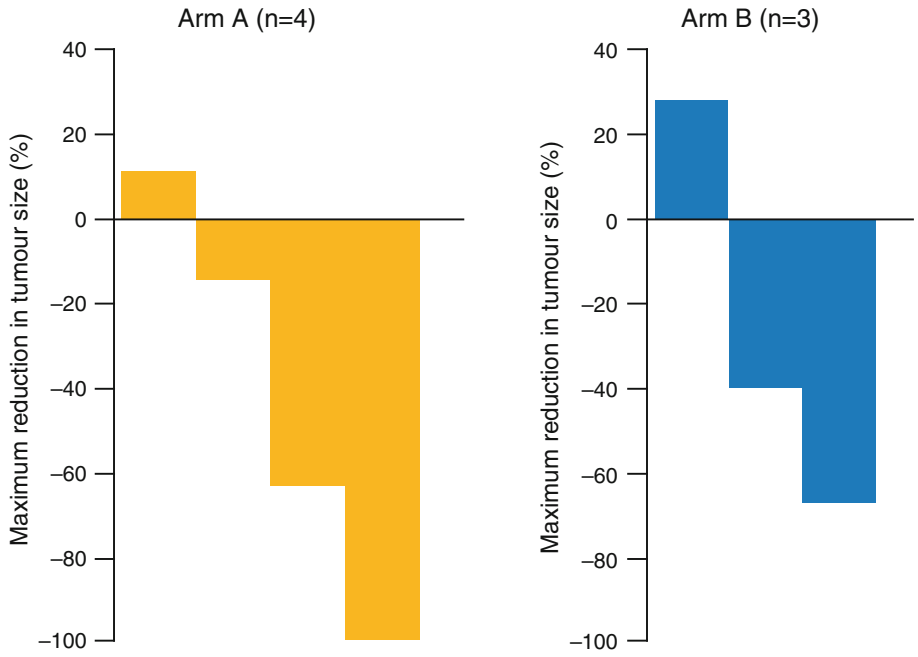

Fig. 2 Waterfall plot for best change in tumour size in each patient

In this small Phase I study, tumour shrinkage was observed in five of seven evaluable patients. This preliminary evidence of antitumour activity is consistent with the efficacy findings observed in an early-phase dose-finding study of sorafenib, a multi-targeted kinase inhibitor with activity versus VEGFR-2 and -3, in combination with capecitabine and cisplatin as a first-line treatment for patients with advanced gastric cancer [32]. However, targeting VEGF signalling with bevacizumab, an anti-VEGF-A monoclonal antibody, in patients with advanced gastric cancer met with disappointing results in the recently reported Phase III AVAGAST study [33]. This first-line study failed to meet its primary endpoint of improved overall survival with the addition of bevacizumab to cisplatin plus capecitabine/5-FU, although an efficacy analysis by geographical region revealed that, for both arms, median overall survival was greatest for patients who enrolled in the Asia/Pacific region. Despite the primary outcome of the AVAGAST study, the bevacizumab regimen showed significant advantages for the secondary efficacy endpoints of progression-free survival and overall response rate, suggesting that anti-VEGF treatment strategies are worthy of continued investigation in advanced gastric cancer.

In conclusion, cediranib 20 mg plus cisplatin and S-1 or capecitabine had a manageable tolerability profile as a first-line treatment in Japanese patients with advanced gastric cancer and showed preliminary evidence of antitumour activity.

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Conflict of interest X.S. and K.H.B. are employees of AstraZeneca and own stock. T.S., Y.Y, K.M., H.H., Y.S., D.T., K.T., T.E.N. and N.B. declare no conflicts of interest.

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