Cancer Chemother Pharmacol (2009) 64:1165–1172
DOI 10.1007/s00280-009-0979-8

ORIGINAL ARTICLE

Phase I, dose escalation and pharmacokinetic study of cediranib (RECENTIN™), a highly potent and selective VEGFR signaling inhibitor, in Japanese patients with advanced solid tumors

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Received: 10 November 2008 / Accepted: 3 March 2009 / Published online: 24 March 2009

Abstract
Purpose To evaluate safety and tolerability of cediranib, a highly potent and selective vascular endothelial growth factor signaling inhibitor, in Japanese patients with advanced solid tumors refractory to standard therapies.
Methods In part A ($n = 16$), patients received once-daily oral cediranib (10–45 mg) to identify the maximum tolerated dose (MTD). In part B ($n = 24$), patients with non-small-cell lung cancer or colorectal cancer received multiple daily doses at the MTD.
Results Cediranib 30 mg/day was considered the MTD since 50% of evaluable patients receiving 45 mg/day experienced dose-limiting toxicities in part A (proteinuria and diarrhea $n = 1$, proteinuria $n = 1$, thrombocytopenia $n = 1$). The most common adverse events were diarrhea ($n = 34$) and hypertension ($n = 32$). Pharmacokinetic analysis confirmed cediranib as suitable for once-daily oral dosing. Of 32 evaluable patients, two had partial RECIST responses and 24 had stable disease ≥8 weeks.
Conclusions Cediranib was generally well tolerated at ≤30 mg/day in these Japanese patients and showed encouraging antitumor activity.

Keywords AZD2171 · Cediranib · Phase I study · Tolerability · Vascular endothelial growth factor receptor

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Introduction

Pathological angiogenesis is a fundamental hallmark of tumor growth and metastasis [1] and therefore a target for the treatment of advanced solid tumors. The vascular endothelial growth factor (VEGF) signaling pathway is recognized as one of the key factors involved in angiogenesis [2]. The VEGF family consists of structurally related dimeric proteins including: VEGF-A, -B, -C, -D and -E, and placental-growth factor. These VEGF ligands bind to one of the three tyrosine kinase receptors (VEGF receptor [VEGFR] -1, -2 and -3) [3, 4]. VEGFR-1 binds VEGF-A, -B and PIGF; VEGFR-2 binds VEGF-A, -C, -D and -E and VEGFR-3 binds VEGF-C and -D. Although VEGF-A binds both VEGFR-1 and -2, the biological effects of VEGF-A are thought to be mediated through binding of VEGFR-2 on vascular endothelial cells resulting in cell survival, proliferation and vascular permeability [5]. VEGFR-3 is expressed on lymphatic endothelial cells where binding of VEGF-C or -D may contribute to metastatic spread through lymphatic vessels. Therefore, inhibition of the VEGFR signaling represents an exciting antitumor strategy [6, 7].

Cediranib (RECENTIN™) is a highly potent and selective VEGF signaling inhibitor with activity against all three VEGFRs. Cediranib potently inhibits the tyrosine kinase

activity associated with VEGFR-2 ($IC_{50} < 0.001$ μM), VEGFR-1 ($IC_{50} = 0.005$ μM) and VEGFR-3 ($IC_{50} \leq 0.003$ μM) and also has activity versus additional structurally related class III receptor tyrosine kinases (c-Kit, PDGFR-β) at low nanomolar concentrations [8]. Broad-spectrum cediranib antitumor activity was observed in preclinical studies in a range of histologically diverse xenograft models [8–10]. Early clinical data from a phase I study in Western patients with a broad range of tumors demonstrated that cediranib was generally well tolerated as monotherapy at doses ≤45 mg and the pharmacokinetic profile supported once-daily oral dosing [11]. The most frequently reported adverse events were fatigue, nausea, diarrhea and hypertension [11].

Other VEGF signaling inhibitors have also demonstrated clinical benefit in various tumor types [12]. In combination with certain chemotherapy regimens, bevacizumab, an anti-VEGF-A monoclonal antibody, demonstrated a survival benefit in metastatic colorectal cancer (CRC) [13] and non-squamous non-small-cell lung cancer (NSCLC) [14, 15]. Sorafenib and sunitinib are small-molecule multitargeted tyrosine kinase inhibitors, with activity against the VEGF signaling pathway and both have demonstrated clinical efficacy as single agents in advanced renal cell carcinoma [16, 17].

The primary objective of this phase I, multicenter, open-label clinical study (study code 2171L0023) was to investigate the safety and tolerability of escalating doses of cediranib in Japanese patients with advanced solid tumors, with the aim of establishing the maximum tolerated dose (MTD) and the recommended dose for phase II studies in Japanese patients. Secondary objectives included evaluation of antitumor activity and assessment of single- and multiple-dose pharmacokinetics. The antitumor activity of cediranib for patients with CRC and NSCLC was exploratory, assessed in the expanded-cohort phase of the study.

Patients and methods

Patients

Adult patients with advanced solid tumors refractory to standard therapies were recruited from a single center in Japan for the dose escalation phase (part A) and two centers in Japan for the expanded-cohort phase (part B) of the study. The expanded-cohort phase (part B) recruited patients with histologically confirmed NSCLC or CRC, refractory to conventional treatment. Subjects were required to have a WHO performance status of 0–2, life expectancy of ≥12 weeks, and normal cardiac, hematopoietic, hepatic and renal function. Patients with poorly controlled hypertension, uncontrolled systemic disease and unresolved toxicity from previous anticancer therapy were excluded from the study. All patients provided written informed consent. The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and the AstraZeneca policy on Bioethics. The final study protocol was approved by an institutional review board in each hospital.

Study design

The primary objective of this phase I, multicenter, open-label study was to assess the safety and tolerability of escalating doses of cediranib. This study, was conducted in two parts: dose escalation phase (part A) and expanded-cohort phase (part B; Fig. 1). In part A, cohorts of at least three patients received a single oral dose of cediranib (10, 20, 30 or 45 mg) followed by a 6–8-day washout period and then subsequent multiple once-daily treatments at the same initial dose. Patients were defined as evaluable if they: (1) completed 75% of the planned daily doses in the first 28 days of the multiple dosing period and had enough information to assess the dose escalation (if less than 75%

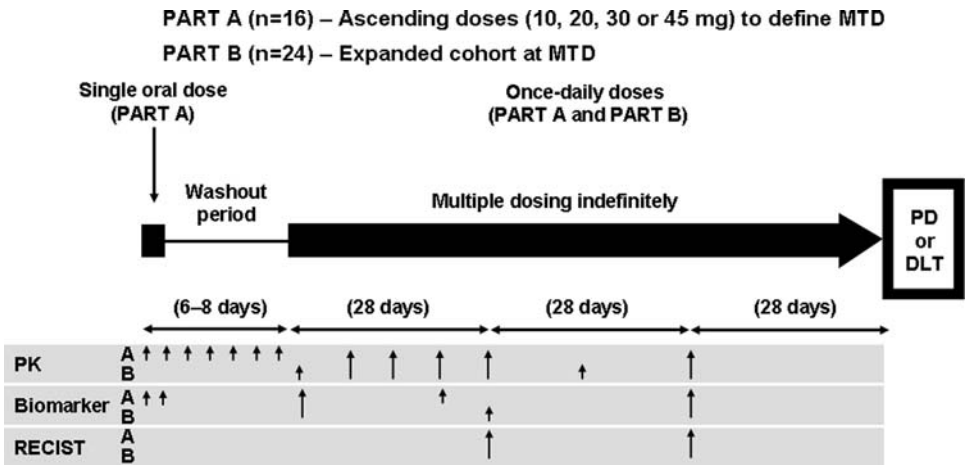


Fig. 1 Study design

compliance and discontinued due to adverse event[s], patients were considered evaluable), or (2) experienced a dose-limiting toxicity (DLT), which was considered by the investigator to be possibly related to cediranib, after the single dose or within the initial 28 days of multiple dosing. If a patient was not evaluable, an additional patient was entered in that dose level.

The primary objective of part A was to establish the MTD for further assessment of biological activity and safety in a separate cohort of patients in part B. Providing <33% of patients experienced a DLT during the first 28 days of multiple dosing, dose escalation was continued. If a DLT was observed in ≥33% to <50% of patients, the cohort was expanded to include a further three patients. If a DLT was observed in ≥50% of patients, this dose was considered above the MTD and dose escalation was stopped. The dose one level below was determined to be the MTD; i.e., the highest dose at which there is a <33% probability of experiencing toxicity within a 28-day cycle. In part B, patients with NSCLC and CRC received once-daily cediranib at the MTD identified in part A. In both parts of the study, treatment continued until evidence of tumor progression or DLT was observed.

A DLT was defined by any of the following adverse events considered by the investigator to be related to cediranib; any adverse event that met the criteria of ≥grade 3 (National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [CTCAE 3.0]); an alanine aminotransferase/aspartate transaminase (ALT/AST) value >200 IU, with the exception of isolated increases in γ-glutamyl transpeptidase (i.e., in the absence of transaminase increase); a QTc increase of >60 ms from baseline to >460 ms, and/or QTc interval of >490 ms on two consecutive electrocardiogram measurements recorded within a 24-h period; and recurrent or persistent increase from baseline in blood pressure of >20 mmHg or to a blood pressure >150/100 mmHg for >24 h. A modified definition of grade 3 hypertension was used (i.e., that which did not respond to per-protocol antihypertensive treatment within 48 h).

Safety and tolerability

Adverse events were recorded throughout the study and graded according to CTCAE 3.0 until resolution or 30 days after the last administration of treatment. Evaluation of the safety and tolerability of oral doses of cediranib was also based on the assessment of laboratory variables; clinical chemistry, hematology and urinalysis.

Pharmacokinetic assessments

Venous blood samples were collected prior to dose and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 and 144 h after a single dose on day 1. In part B, samples were collected from the first six patients each in both NSCLC and CRC groups; prior to dosing and then 1, 2, 3, 4, 6, 8, 12 and 24 h after administration on day 28 after multiple doses. All samples were analyzed for cediranib using high performance liquid chromatography with tandem mass spectrometry (HPLC-MS-MS). These data were used to calculate cediranib maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the curve to infinity ($AUC_{(0-\infty)}$) and half-life associated with terminal slope of a semi-logarithmic concentration-time curve ($t_{½\lambda z}$) in the single-dose phase of part A. Maximum plasma drug concentration at steady state ($C_{ss,max}$), minimum plasma drug concentration at steady state ($C_{ss,min}$), t_{max}, area under the curve at steady state (AUC_{ss}), were calculated from multiple dosing phases in both parts A and B and accumulation ratio (R_{ac}) and temporal change parameter (TCP) calculated in the multiple dosing phase of part A only. All parameters were estimated using standard noncompartmental methods [11].

Tumor response evaluation

Baseline tumor assessments were performed 2 weeks or less before the planned first dose or within 28 days before the first dose (day 1) if the tumor assessment was obtained before consent. Subsequent assessments were scheduled following 28 days of daily dosing and every 4 weeks thereafter. Objective tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) [18].

Statistical considerations

No formal statistical analysis was performed. Safety data were summarized using descriptive statistics and pharmacokinetic data were summarized using the geometric mean, CV (coefficient of variation), mean, standard deviation, minimum, maximum and *n*.

Results

Patient characteristics

A total of 40 patients from two centers in Japan (16 patients in part A and 24 patients in part B) were enrolled (Table 1). A total of 17 patients were ongoing in the study at the time of database lock; 5 (31%) patients in part A and 12 (50%) patients in part B. Among the 23 discontinued patients, the most common reason for discontinuation was condition under investigation worsened (15/23 [65.2%]) and adverse events (3/23 [13.0%]).

Table 1 Patient characteristics

	Part A ($n = 16$)	Part B ($n = 24$)	Total ($n = 40$)
Age, years			
Mean	46	62	55
Range	26–73	34–73	26–73
Sex, *n* (%)			
Male	9 (56.3)	15 (62.5)	24 (60.0)
Female	7 (43.8)	9 (37.5)	16 (40.0)
WHO performance status, *n* (%)			
0	6 (37.5)	7 (29.2)	13 (32.5)
1	10 (62.5)	17 (70.8)	27 (67.5)
Primary tumor diagnosis, *n* (%)			
NSCLC	5 (31.3)	12 (50.0)	17 (42.5)
Colon	3 (18.8)	6 (25.0)	9 (22.5)
Rectum	2 (12.5)	6 (25.0)	8 (20.0)
Skin/soft tissue	2 (12.5)	0 (0.0)	2 (5.0)
Ovary	1 (6.3)	0 (0.0)	1 (2.5)
Stomach sarcoma	1 (6.3)	0 (0.0)	1 (2.5)
Thymus	2 (12.5)	0 (0.0)	2 (5.0)
Previous treatment, *n* (%)			
Chemotherapy	15 (93.8)	24 (100.0)	39 (97.5)
1–2 regimens	6 (37.5)	12 (50.0)	18 (45.0)
≥3 regimens	9 (56.3)	12 (50.0)	21 (52.5)
Radiotherapy	8 (50.0)	6 (25.0)	14 (35.0)
Surgery	12 (75.0)	16 (66.7)	28 (70.0)

NSCLC non-small-cell lung cancer

Safety and tolerability

In part A, three (50%) of six evaluable patients in the 45 mg group experienced a DLT (proteinuria and diarrhea $n = 1$, proteinuria $n = 1$, thrombocytopenia $n = 1$); therefore cediranib 30 mg was determined as the MTD in this patient population. One patient in the 45 mg group was not evaluable for the safety analyses due to receiving other therapy for bone metastasis. In both part A and part B, the most commonly occurring adverse events were diarrhea ($n = 34$), hypertension ($n = 32$), palmar–plantar erythrodysesthesia (PPE [hand–foot syndrome]) ($n = 27$) and fatigue ($n = 26$) (Table 2a). There were no incidences of hypertension grade 3 or higher in this study. Among the 32 patients who received antihypertensive drugs during the course of the study, 4 required additional antihypertensive therapy and 5 patients required dose increases of existing antihypertensive medication. The most common laboratory abnormalities were increased blood erythropoietin ($n = 29$), increased blood thyroid-stimulating hormone (TSH) ($n = 28$) and proteinuria ($n = 27$) (Table 2b). Although blood TSH increases were reported in the majority of patients, no patients were symptomatic for hypothyroidism and none required replacement therapy with thyroxine. The majority of adverse events were grade 1 or 2. The incidence of grade 3 or 4 adverse events and laboratory abnormalities were low; the most common (≥10%) being diarrhea ($n = 4$), neutropenia ($n = 3$) and proteinuria ($n = 4$). A total of nine patients (1 [6%], 8 [33%] in part A and part B, respectively) experienced at least one serious adverse event, including proteinuria ($n = 3$), abdominal abscess, abnormal hepatic function, colitis, increased blood creatine phosphokinase, liver disorder, lung infection, nephritic syndrome, pneumonia, sepsis and thrombocytopenia (all $n = 1$) in part B, and pneumothorax ($n = 1$) in part A. There were no serious adverse events reported at cediranib doses <30 mg. In part A, dose reductions occurred in 1/3 patients in the 30 mg cohort and in 4/7 patients in the 45 mg cohort; 7/24 patients in Part B required a dose reduction.

Pharmacokinetic assessments

Plasma concentration–time profiles are shown in Fig. 2a and b for single and multiple dosing in part A, respectively. C_{max} was achieved 1.9–4.0 h after dosing for each dose level. After attaining C_{max}, plasma concentration declined in an apparent bi-exponential manner thereafter, with a mean $t_{½λz}$ ranging from 19.0 to 27.9 h. For all dose levels, accumulation was consistent with the $t_{½λz}$ observed following single doses as was the prediction of steady-state cediranib plasma concentration. The mean value of TCP ranged from 0.99 to 1.31, supporting no time-dependent changes in pharmacokinetics. Steady state was attained after ~7 days of once-daily dosing. Following multiple oral dosing of cediranib 20 and 30 mg, the unbound $C_{ss,min}$ was 3.8 and 5 times above the human umbilical vein endothelial cell (HUVEC) proliferation IC_{50}, respectively.

Tumor response evaluation

Of 32 evaluable patients (10 in part A, and 22 [12 with CRC and 10 with NSCLC] in part B) with baseline RECIST data, two confirmed partial responses (PR) were observed; one in a patient with alveolar soft tissue sarcoma (45 mg, part A) and one with CRC (30 mg, part B). Twenty-four patients had stable disease (SD ≥8 weeks); eight patients in part A including all three patients who received 10 mg (NSCLC [$n = 4$], CRC [$n = 2$], ovary [$n = 1$] and stomach [$n = 1$]) and 16 patients in part B (CRC [$n = 9$] and NSCLC [$n = 7$]). Disease control rate was 81% (26/32). The best overall responses are summarized in Table 3. One patient with NSCLC (30 mg) in part B experienced a best overall response of SD up to data

Table 2 Safety and tolerability (a) clinical adverse events and (b) laboratory abnormalities, irrespective of causality, reported in >30% of patients (the numbers in parentheses refer to adverse events (a) or laboratory abnormalities (b) classified as grade 3/4)

MedDRA-preferred term[a]	Part A				Part B (30 mg)		Total (n = 40)
	10 mg (n = 3)	20 mg (n = 3)	30 mg (n = 3)	45 mg (n = 7)	CRC (n = 12)	NSCLC (n = 12)	
a. Clinical adverse events							
Diarrhea	2 (1/0)	3	3	6 (2/0)	9	11 (1/0)	34 (4/0)
Hypertension	1	3	2	6	10	10	32
PPE syndrome	2	3 (1/0)	3	3	9	7	27 (1/0)
Fatigue	2	2	2	6	7 (1/0)	7	26 (1/0)
Anorexia	2	2	2	5	6	3	20
Dysphonia	0	1	2	1	3	10	17
Nausea	2	0	1 (1/0)	4	5	2	14 (1/0)
Constipation	2	0	1	3	5	2	13
Headache	1	1	1	3	6	1	13
b. Laboratory abnormalities							
Increased blood erythropoietin	3	3	2	7	7	7	29
Increased blood TSH	1	3	3	5	8	8	28
Proteinuria	2	2	1	6 (2/0)	10 (1/1)	6	27 (3/1)
Increased ALT	0	2	1	6	3	3	15
Increased AST	0	2	2	6	2	3	15
Blood urine present	1	1	0	4	4	4	14
Thrombocytopenia	0	0	1	4 (1/0)	6 (1/0)	3	14 (2/0)
Neutropenia	0	3	1 (1/0)	3 (0/1)	4 (1/0)	2	13 (2/1)
Leukopenia	0	2	1	3 (0/1)	5	2	13 (0/1)

PPE palmar–plantar erythrodysesthesia (hand–foot syndrome), *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *TSH* thyroid-stimulating hormone

[a] MedDRA version 10.0

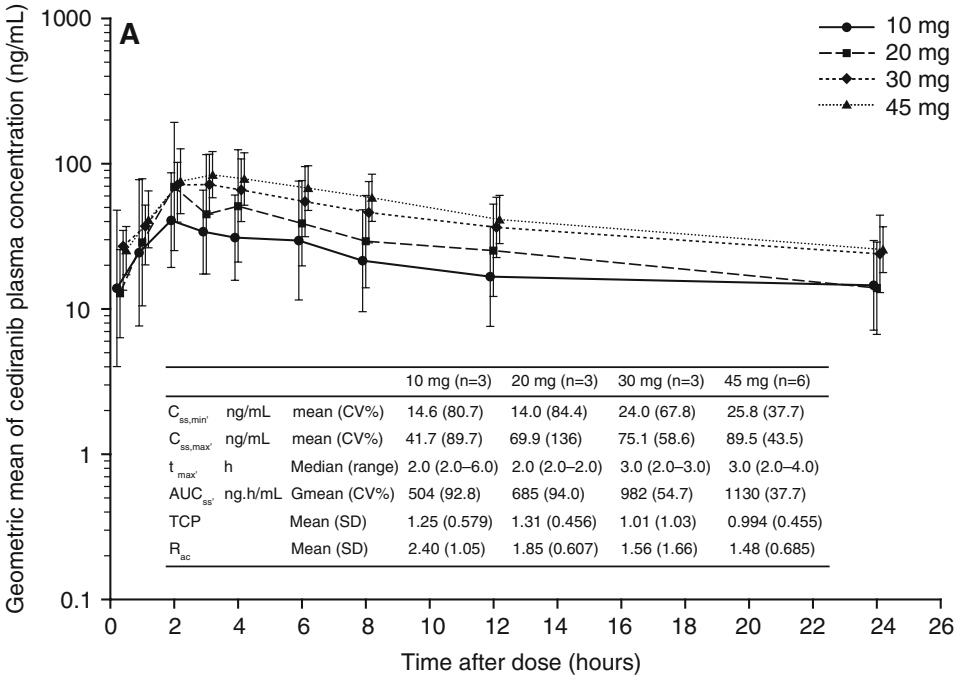
cut-off, but subsequently achieved a PR (Fig. 3a). The majority of patients showed some reduction in tumor size during the study, shown in the waterfall plot (Fig. 3b). Of all 16 patients in part A, 6 (PR [n = 1], SD [n = 1] and non-evaluable [n = 4]) continued to receive treatment with cediranib for over 1 year. Among the 12 patients in Part B ongoing at data cut-off, 6 had received treatment for at least 6 months.

Discussion

In this phase I dose-escalation study, treatment with cediranib ≤30 mg/day was generally well tolerated, with a manageable adverse event profile, and showed encouraging antitumor activity in this population of Japanese patients.

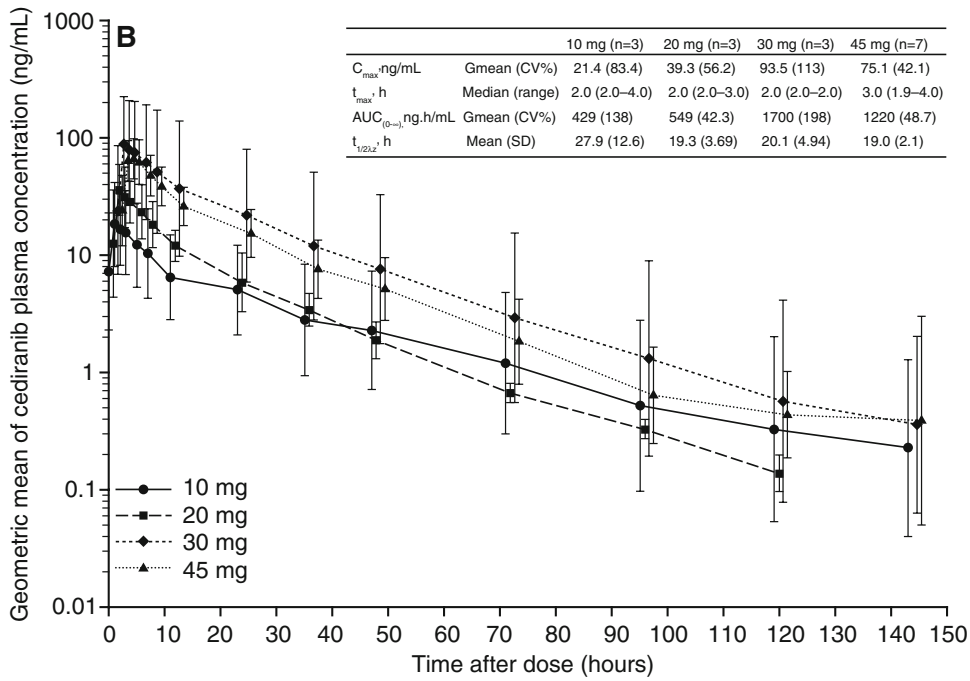
The most frequently reported adverse events of any grade were diarrhea, fatigue and hypertension. The majority of adverse events were transient grade 1 or 2 with a few cases of grade 3 or higher, all of which were manageable. The most common laboratory test abnormalities were increased blood erythropoietin, increased blood TSH and proteinuria. DLTs experienced in part A at 45 mg were diarrhea, proteinuria and thrombocytopenia. Overall, the adverse event profile was broadly consistent with that in the Western population [11].

Although hypertension was a commonly reported adverse event, all incidences were graded ≤2 and no serious adverse events due to hypertension were observed. This is in contrast to the findings of the phase I study of cediranib in a Western population, where hypertension was the most common DLT with cediranib 20 mg or higher [11]. This may be due to successful implementation of a standardized hypertension management protocol in this study [19]. Hypertension is most likely due to the potent inhibitory effect of cediranib on VEGF signaling [20]. The vasodilatory effects of VEGF are thought to be mediated via downstream nitric oxide signaling, although prostacyclin may also play a role [20]. Inhibition of the VEGF-induced vasodilation, principally through VEGF/VEGFR-2 signaling, can increase vasoconstriction and induce hypertension [21]. Hypertension has been observed in both preclinical [20] and other clinical studies [11], with cediranib as well as with other small-molecule VEGFR tyrosine kinase inhibitors [22–25].



			10 mg (n=3)	20 mg (n=3)	30 mg (n=3)	45 mg (n=6)
$C_{ss,min}$	ng/mL	mean (CV%)	14.6 (80.7)	14.0 (84.4)	24.0 (67.8)	25.8 (37.7)
$C_{ss,max}$	ng/mL	mean (CV%)	41.7 (89.7)	69.9 (136)	75.1 (58.6)	89.5 (43.5)
t_{max}	h	Median (range)	2.0 (2.0–6.0)	2.0 (2.0–2.0)	3.0 (2.0–3.0)	3.0 (2.0–4.0)
AUC_{ss}	ng.h/mL	Gmean (CV%)	504 (92.8)	685 (94.0)	982 (54.7)	1130 (37.7)
TCP		Mean (SD)	1.25 (0.579)	1.31 (0.456)	1.01 (1.03)	0.994 (0.455)
R_{ac}		Mean (SD)	2.40 (1.05)	1.85 (0.607)	1.56 (1.66)	1.48 (0.685)

AUC , area under plasma concentration-time curve at steady state; $C_{ss,min}$ minimum, and $C_{ss,max}$, maximum plasma drug concentration at steady state; CV%, coefficient of variation; t_{max} , time of maximum observed concentration; TCP, temporal change parameter (day 28 AUC_{ss} of cycle 1/$AUC_{(0-\infty)}$ of cycle 0) R_{ac}, accumulation ratio (day 28 AUC_{ss} of cycle 1/$AUC_{(0-24)}$ of cycle 0)



		10 mg (n=3)	20 mg (n=3)	30 mg (n=3)	45 mg (n=7)
C_{max},ng/mL	Gmean (CV%)	21.4 (83.4)	39.3 (56.2)	93.5 (113)	75.1 (42.1)
t_{max}, h	Median (range)	2.0 (2.0–4.0)	2.0 (2.0–3.0)	2.0 (2.0–2.0)	3.0 (1.9–4.0)
$AUC_{(0-\infty)}$,ng.h/mL	Gmean (CV%)	429 (138)	549 (42.3)	1700 (198)	1220 (48.7)
$t_{1/2\lambda z}$, h	Mean (SD)	27.9 (12.6)	19.3 (3.69)	20.1 (4.94)	19.0 (2.1)

AUC_{ss} area under plasma concentration-time curve at steady state; C_{max} maximum plasma drug concentration; CV%, coefficient of variation; t_{max} time of maximum observed concentration; TCP, temporal change parameter (day 28 AUC_{ss} of cycle 1/$AUC_{(0-\infty)}$ of cycle 0); R_{ac}accumulation ratio (day 28 AUC_{ss} of cycle 1/$AUC_{(0-24)}$ of cycle 0)

Fig. 2 Geometric mean plasma concentration and pharmacokinetic parameter estimates after, **a** a single dose of cediranib, **b** multiple doses of cediranib in part A

The MTD of cediranib in this population of Japanese patients was 30 mg, which was less than the MTD determined in the first clinical study of cediranib in a Western population of 45 mg [11]. However, this comparison is based on small patient numbers and in the Western study many of the patients receiving an initial dose of cediranib 45 mg did, in fact, undergo dose reductions to 30 mg. Moreover, in subsequent studies in Western patients, cediranib 45 mg monotherapy was not adequately tolerated and the study protocols have been amended to reduce the dose to cediranib 30 mg [26, 27].

Table 3 Best overall response (RECIST)

	Part A				Part B (30 mg)		Total (n = 40)
	10 mg (n = 3)	20 mg (n = 3)	30 mg (n = 3)	45 mg (n = 7)	CRC (n = 12)	NSCLC (n = 12)	
Complete response	0	0	0	0	0	0	0
Partial response	0	0	0	1	1	0	2
Stable disease ≥8 weeks	3	1	1	3	9	7	24
Progressive disease	0	0	0	1	1	3	5
Not evaluable[a]	0	0	0	0	1	0	1
Not applicable for RECIST[b]	0	2	2	2	0	2	8

[a] Patient had RECIST data at baseline but withdrew 4 days after treatment due to an adverse event (hepatic function abnormality)

[b] Patient had no RECIST data (measurable lesion) at baseline

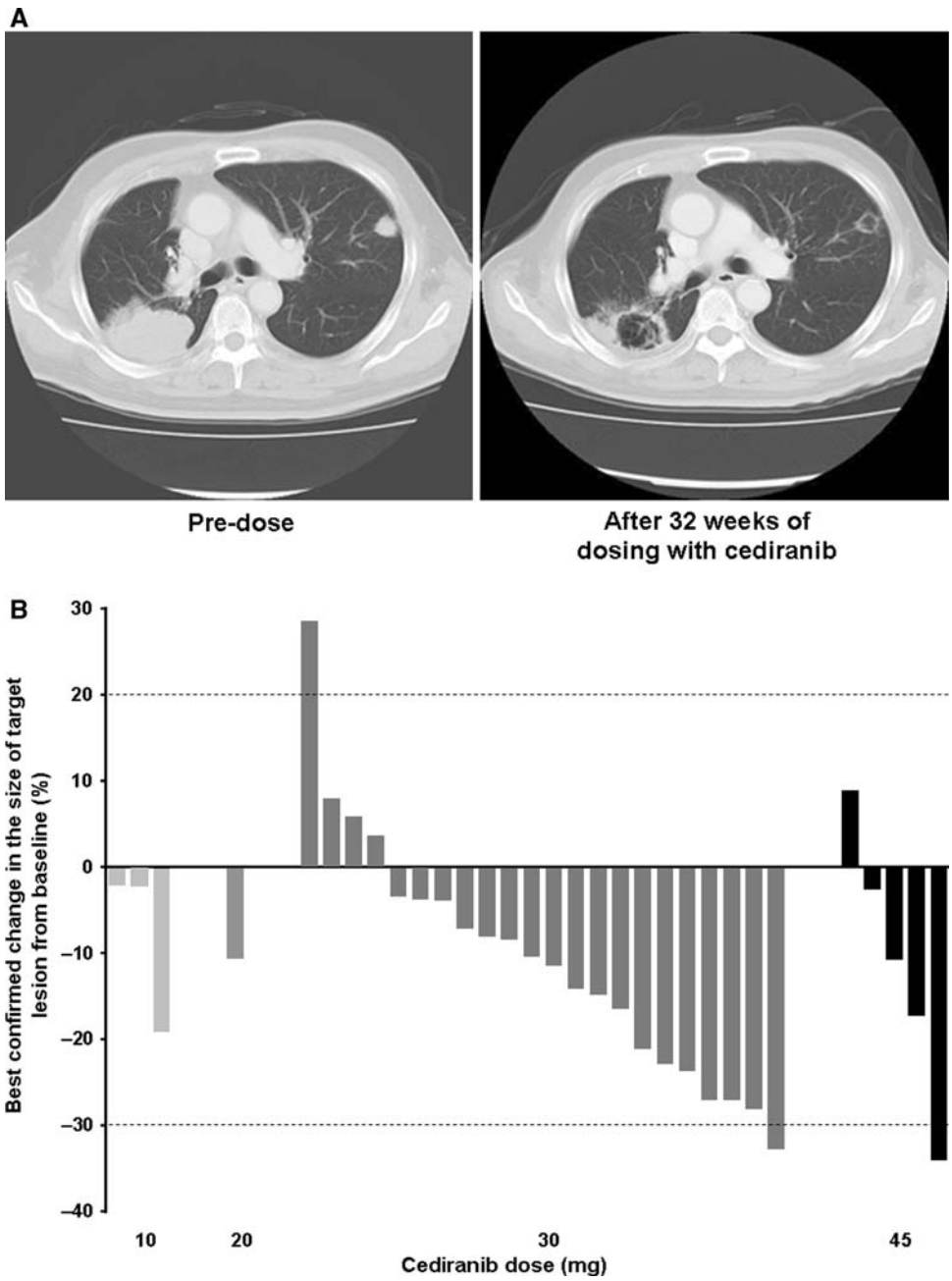


Fig. 3 Tumor response evaluation. **a** Partial response in a male patient (aged 72 years) with NSCLC after 32 weeks of dosing with cediranib. **b** Waterfall plot of percentage change in tumor size at maximum reduction by dose. Each *bar* represents one patient; *dotted lines* represent the boundaries for progressive disease (20%) and partial response (−30%)

Pharmacokinetic assessment confirmed that cediranib is suitable for once-daily oral dosing with C_{max} achieving a range from 1.9 to 4.0 h and $t_{½λz}$ ranging from 19.0 to 27.9. After multiple dosing at 20 mg, the unbound $C_{ss,min}$ was 3.85 times higher than the HUVEC proliferation IC_{50}. Both single- and multiple-dose pharmacokinetic parameters were similar to those observed in the Western population [11].

This study was designed primarily to investigate the safety and tolerability profile of cediranib monotherapy. However, there was encouraging preliminary evidence of antitumor activity in this population of Japanese patients. The majority of patients had some tumor reduction during the study, including two confirmed PRs and 24 patients with SD (≥8 weeks). At data cut-off, 6 out of 16 patients from part A of the study were continuing to receive cediranib monotherapy for ≥1 year.

In conclusion, once-daily oral administration of cediranib monotherapy at doses ≤30 mg/day is generally well tolerated in Japanese patients with advanced solid tumors. Cediranib is currently in phase III development in patients with CRC and glioblastoma. The potential utility of cediranib (as a single agent and in combination) also continues to be investigated in a range of other tumors.

Acknowledgments This study, including medical writing support provided by Rebecca Helson of Mudskipper Bioscience, was supported financially by AstraZeneca. RECENTIN™ is a trade mark of the AstraZeneca group of companies. Noboru Yamamoto and Tomohide Tamura have received remuneration from AstraZeneca KK and Eisei Shin has stock ownership.

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