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Phase I evaluation of cediranib, a selective VEGFR signalling inhibitor, in combination with gefitinib in patients with advanced tumours

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ARTICLE INFO

Article history:
Received 23 September 2009
Received in revised form 7 December 2009
Accepted 14 December 2009
Available online 12 January 2010

Keywords:
VEGFR-1
VEGFR-2
VEGFR-3
EGFR
Angiogenesis inhibitors
Clinical trial
Phase I

ABSTRACT

Aim: Cediranib is a highly potent inhibitor of vascular endothelial growth factor receptor (VEGFR) signalling. Preclinical and clinical data suggest that inhibition of the VEGFR and epidermal growth factor receptor (EGFR) pathways may be synergistic. Combination treatment with cediranib and gefitinib, an EGFR signalling inhibitor, was evaluated in patients with advanced solid tumours.

Patients and methods: Ninety patients received treatment in this four-part, open-label study (NCT00502060). The patients received once-daily oral doses of cediranib (20–45 mg) and gefitinib 250 mg (part A1; $n = 16$) or 500 mg (part B1; $n = 44$). A cohort expansion phase investigated the potential pharmacokinetic interaction of cediranib 30 mg with gefitinib 250 mg (part A2; $n = 15$) or 500 mg (part B2; $n = 15$). The primary objective was to assess the safety and tolerability of cediranib with gefitinib. Secondary assessments included pharmacokinetics, efficacy and pharmacodynamics.

Results: Combination treatment was generally well tolerated; the protocol-defined maximum-tolerated dose of cediranib was 30 mg/day with gefitinib 250 mg/day (part A1) and cediranib 45 mg/day was the maximum dose investigated with gefitinib 500 mg/day (part B1). The most common adverse events were diarrhoea (84 [93%]), anorexia (63 [70%]) and fatigue (60 [67%]). Cediranib pharmacokinetic parameters were not substantially different when given alone or in combination with gefitinib. Gefitinib pharmacokinetic parameters were similar to those seen previously with gefitinib monotherapy. Efficacy results included eight (9%) confirmed partial responses (6 renal; 1 lung; 1 osteosarcoma) and 38 (42%)

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doi:10.1016/j.ejca.2009.12.023

patients with stable disease. Pharmacodynamic assessments demonstrated changes in levels of VEGF and soluble VEGFR-2 following treatment.

Conclusions: Combination treatment was generally well tolerated and showed encouraging antitumour activity in patients with advanced solid tumours. These results merit further exploration.

1. Introduction

Vascular endothelial growth factor (VEGF) is a key factor in tumour-associated angiogenesis, and exerts its effects via three high-affinity receptors: VEGFR-1, VEGFR-2, both present on vascular endothelium and VEGFR-3, present on lymphatic endothelium. VEGFR-2 appears to play a predominant role in tumour-associated angiogenesis and is considered an important target for the inhibition of tumour growth.[1] The epidermal growth factor receptor (EGFR) tyrosine kinase is expressed at high levels in most human solid tumours and has been associated with progression and poor prognosis in non-small-cell lung cancer (NSCLC).[2,3] In addition, EGFR signalling has also been shown to be involved in tumour–host interactions such as angiogenesis.[4]

Since tumour growth and progression depend on tumour–host interactions as well as tumour cell characteristics,[5] combining inhibition of VEGFR- and EGFR-dependent signalling may be a useful approach to treating cancer. Preclinical data suggest that concomitant targeting of the VEGFR and EGFR signalling pathways may lead to greater antitumour activity than inhibition of either pathway alone.[4,6,7] Furthermore, the results of a recent Phase II study in advanced NSCLC support the combined use of anti-VEGF (bevacizumab) and anti-EGFR (erlotinib) therapy compared with chemotherapy alone.[8]

Cediranib (RECENTIN™) is a highly potent inhibitor of all three VEGFRs (VEGFR-1, -2 and -3) with a pharmacokinetic profile that is suitable for continuous once-daily oral dosing.[9,10] This in contrast to bevacizumab, which sequesters the VEGF-A ligand and therefore has no effect on the VEGF-3-dependent signalling pathway[11] VEGFR-3, largely located on lymphatic vessels, may play an important role in the regulation of lymphangiogenesis,[12] and has recently also been shown to be involved in angiogenesis.[13] In addition, the oral bioavailability and shorter half-life of cediranib may provide more flexible dosing than bevacizumab ($t_{1/2} \sim 3$ weeks)[14] in the event of toxicity. The continuous once-daily dosing regimen for cediranib also differentiates it from the orally available VEGFR tyrosine kinase inhibitors that have received regulatory approval; sorafenib is given twice daily and sunitinib is given once-daily as part of a 6-week dosing cycle (4 weeks on/2 weeks off). Cediranib has shown broad-spectrum antitumour activity in a range of histologically diverse xenograft models.[9] During early clinical evaluation, cediranib monotherapy was generally well tolerated at doses $\geqslant$45 mg. The most common adverse events (AEs) were fatigue, hypertension and gastrointestinal toxicity, and dose-limiting toxicities (DLTs) were hypertension and diarrhoea. There was also encouraging evidence of antitumour activity and the pharmacokinetic profile supported a once-daily oral dosing regimen.[10]

Gefitinib (IRESSA™) is an EGFR tyrosine kinase inhibitor that has demonstrated non-inferiority relative to docetaxel in terms of overall survival in unselected patients with pretreated advanced NSCLC in the recently reported Phase III INTEREST study.[15]

The primary objective of the present study was to assess the safety and tolerability of combination therapy with cediranib and gefitinib in patients with advanced cancers. Secondary objectives included an investigation of the pharmacokinetics of cediranib given alone or in combination with gefitinib, a preliminary assessment of the antitumour activity of this regimen, and an exploration of the effects of treatment on biological markers.

2. Patients and methods

2.1. Patient eligibility

Patients with advanced cancer refractory to standard treatment were recruited to one of the three centres in the Netherlands. The patients were required to have a life expectancy of at least 12 weeks and a World Health Organisation performance status of 0–2. The main exclusion criteria were inadequate bone marrow reserve; renal or hepatic dysfunction and poorly controlled hypertension. Written informed consent was provided by all patients. The trial was approved by all relevant institutional ethical committees or review bodies, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

2.2. Study design

This was an open-label, multicentre study conducted in four-parts (Fig. 1; study code 2171IL0004). The first part of the study was a dose-escalation phase in which successive cohorts of 3–8 patients (to ensure at least three evaluable) received fixed oral doses of cediranib (20–45 mg/day) combined with fixed oral doses of gefitinib 250 mg/day (part A1) or 500 mg/day (part B1). For part A1 the starting dose of cediranib 20 mg was selected based on the safety, tolerability and biological activity data from a previous cediranib monotherapy study.[10] The starting dose for part B1 was protocolled to be below the maximum-tolerated dose (MTD) of cediranib identified in part A1.

To identify the MTD of cediranib with gefitinib 250 mg or 500 mg in parts A1 and B1, safety evaluation meetings were held once a minimum of three patients in a cohort were considered to be evaluable. To be evaluable a patient must have completed 21 days of continuous daily treatment or experienced a dose-limiting toxicity (DLT) within the 21-day evaluation period. Providing <33% of the evaluable patients had

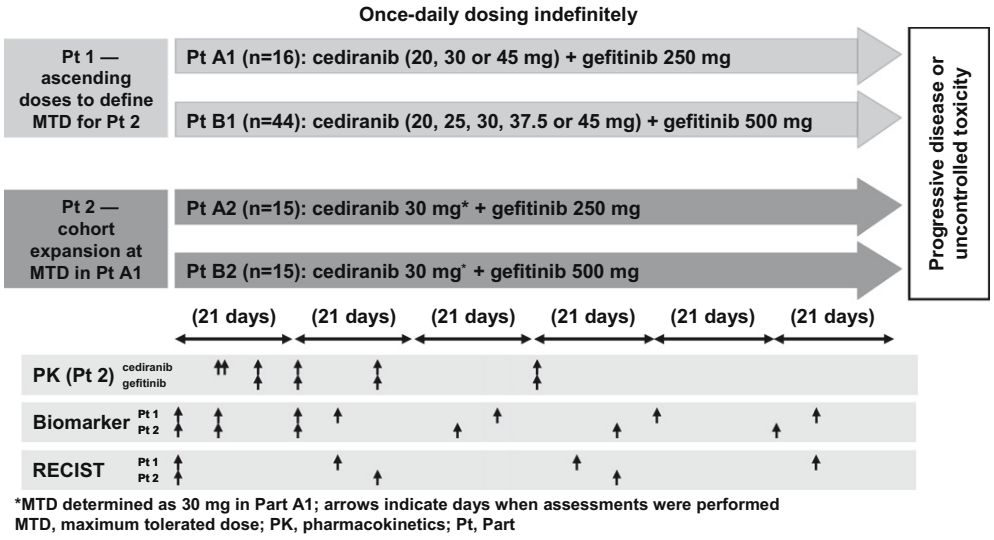


Fig. 1 – Study design.

experienced a DLT, the dose was defined as tolerable and dose escalation could continue. If a DLT was observed in ⩾33% to <50% of patients, the cohort was expanded so that a further three patients would be included in the safety review. If a DLT was observed in ⩾50% of patients, this dose was considered above the MTD; the dose one level below would be considered to be the MTD. Once the MTD had been defined in parts A1 and B1, the pharmacokinetics of cediranib were explored alone and in combination with gefitinib in the cohort expansion part of the study. The patients (15 per cohort) received once-daily cediranib as monotherapy for 7 days and then in combination with gefitinib 250 mg (part A2) or 500 mg (part B2) for 14 days.

2.3. *Safety and tolerability*

A DLT was defined, occurring within the 21-day evaluation period: any AE of grade 3 or higher (using the National Cancer Institute Common Terminology Criteria [CTC] version 3.0 or the modified CTC grading for hypertension as described previously[10]); that was not clearly related to disease progression and was considered by the investigator to be related to one or both study treatments. An exception was made for AEs of rash and diarrhoea, which were known to be commonly associated with gefitinib treatment. If the DLT was rash or diarrhoea, the safety committee could consider whether the frequency of these events was greater than that expected to be observed with gefitinib alone from experience and historical data, in order to make the dose-escalation decision for cediranib in the combination therapy.

Blood samples for the determination of clinical chemistry and haematology parameters were taken on day 1 and weekly for the first 4 weeks in part A1/B1, 3 weeks in part A2/B2 and every 2 weeks thereafter. Systolic and diastolic blood pressure (SBP and DBP, respectively) measurements were taken at baseline and day 1 (pre-dose and up to 24 h post-dose) and every 7 days thereafter.

2.4. *Pharmacokinetic assessments*

In parts A2/B2, the blood samples were collected for the determination of plasma levels of cediranib and gefitinib at the timepoints indicated in Fig. 1. Plasma concentrations of cediranib and gefitinib were analysed using high-performance liquid chromatography with tandem mass spectrometric (HPLC–MS–MS) detection. Maximum and minimum steady-state drug concentration ($C_{max,ss}$ and $C_{min,ss}$), and the time to reach maximal concentration (t_{max}) were determined by visual inspection of the individual plasma concentration–time profiles. The area under the plasma profiles at steady-state (AUC_{ss}) was estimated by the linear trapezoidal algorithm to the last data point of the dosing interval.

2.5. *Tumour response evaluation*

Tumour response was evaluated according to Response Evaluation Criteria in Solid Tumours (RECISTs).[16] Baseline imaging was performed no more than 4 weeks before the start of the study treatment. Subsequent assessments were performed 4 weeks (part 1)/5 weeks (part 2) from the start of the treatment and every 6 weeks thereafter.

2.6. *Pharmacodynamic analyses*

Serum and plasma samples were collected at the times shown in Fig. 1 for the measurement of surrogate markers of angiogenesis and activated endothelial cells. VEGF and basic fibroblast growth factor (bFGF) were measured in plasma samples, while soluble VEGFR-2 (sVEGFR-2) and soluble tunica interna endothelial cell kinase (sTie-2) were measured in serum. Parameters were determined as described previously.[10]

2.7. *Statistical analyses*

There was no formal statistical analysis for the assessments of safety and tolerability. Response data were listed and sum-

marised. Biomarker data were plotted and summarised as appropriate.

Pharmacokinetic data collected in parts A2 and B2 were $\log_e$-transformed and analysed separately and combined using a paired *t*-test. The results were then back-transformed to provide a point estimate and the corresponding two-sided 90% confidence interval (CI) for the ratio (cediranib + gefitinib/cediranib). The intent of this analysis was to estimate the effect of gefitinib on the pharmacokinetics of cediranib in order to support the safety and tolerability conclusions, and not to formally demonstrate any clinically meaningful effect of gefitinib on the pharmacokinetics of cediranib.

3. Results

3.1. Patient characteristics

Between May 2004 and February 2006, 92 patients were enrolled into the study and of these 90 received treatment and were included in the safety analysis (Table 1). Two patients did not receive treatment due to AEs, which occurred prior to the first cediranib dose. At the time of data cutoff (August 2006) the mean duration of treatment was 113.9 days (range 2–395) in part A and 144.7 days (range 12–365) in part B, with 12 patients still on treatment at the time of database lock.

3.2. Safety and tolerability

Overall, the most frequent AEs in both parts of the study were diarrhoea, anorexia and fatigue (Table 2a). These were also among the most common AEs considered to be related to either treatment. The other most common AEs attributed by the investigator to study treatment were hypertension (cediranib) and rash and dry skin (both gefitinib).

AEs that met the criteria for DLT in parts A1 and B1 are listed in Table 2b. In part A1, no patients in the cediranib 20 mg group experienced a DLT; 1/5 patients (20%) experienced a DLT of hypertension in the cediranib 30 mg cohort and 3/8 patients (38%) enrolled in the cediranib 45 mg cohort experienced five DLTs. On the basis of the number of DLTs in part A1 at 45 mg reported in evaluable patients at the time of the safety review meeting, the MTD of cediranib was identified as 30 mg in combination with gefitinib 250 mg.

In part B1, in the first cohort with 20 mg, 3/8 patients (38%) experienced six grade 3 AEs; all three patients experienced events of diarrhoea, which were attributed to the higher dose of gefitinib. Therefore dose escalation was allowed to continue but at a slower rate than in part A1. Once cediranib 30 mg was declared tolerable in part B1, this dose was taken forward into part B2. At that time, the protocol prevented the dose in part B1 being escalated above 30 mg as it was the MTD from part A1 but, since cediranib 30 mg was considered to be well tolerated in part B1 and the overall DLT rate for

Table 1 – Patient characteristics.

Study part	A1			A2			B1			B2	Total
Cediranib dose, mg	20	30	45	30	20	25	30	37.5	45	30	
Gefitinib dose, mg	250	250	250	250	500	500	500	500	500	500	
Number of patients, *n*	3	5	8	15	8	8	8	13	7	15	90
Age, years											
Mean	46	46	56	57	58	54	49	59	58	49	54
Range	33–66	31–60	40–66	35–78	47–73	32–73	22–65	42–77	44–71	30–70	22–78
Sex, n											
Male	3	3	5	12	7	6	5	7	6	11	65
Female	0	2	3	3	1	2	3	6	1	4	25
Race											
Caucasian	3	5	8	15	8	8	8	13	7	15	90
Primary tumour type											
Renal	–	–	–	2	3	2	2	2	3	4	18
Colorectal	1	1	2	4	2	–	1	4	2	–	17
Lung[a]	–	2	2	–	2	2	–	2	1	3	14
Skin/soft tissue	–	–	1	2	–	–	4	1	–	4	12
Stomach	–	–	–	2	–	–	–	–	–	1	3
Bone	–	1	–	–	–	–	1	–	–	–	2
Pleura	–	–	–	1	1	–	–	–	–	–	2
Head and neck	–	–	–	1	–	–	–	1	–	–	2
Breast	–	–	1	–	–	–	–	–	–	–	1
Pancreas	–	–	1	–	–	–	–	–	–	–	1
Prostate	–	–	–	1	–	–	–	–	–	–	1
Oesophagus Bladder	–	–	–	–	–	1	–	–	–	–	1
Peritoneum	–	–	–	–	–	–	–	1	–	–	1
Other	–	–	–	–	–	–	–	1	–	–	1
	2	1	1	2	–	3	–	1	1	3	14

a Histologies include non-small-cell lung cancer (*n* = 7), broncoalveolar cell carcinoma (*n* = 2), mesothelioma (*n* = 2), pancoast (*n* = 1), and lung not otherwise specified (*n* = 2).

Table 2 – Adverse events. (a) Number of patients (%) with adverse events occurring during treatment (⩾15%), irrespective of causality. (b) Number of patients with adverse events meeting dose-limiting toxicity criteria[a] in part A1 and B1 (all grade 3).

Study part	A1			A2		B1				B2	Total, *n* (%)
(a)											
Cediranib dose, mg	20	30	45	30	20	25	30	37.5	45	30	
Gefitinib dose, mg	250	250	250	250	500	500	500	500	500	500	
Number of patients, *n*	3	5	8	15	8	8	8	13	7	15	90 (100)
Diarrhoea	3 (100)	4 (80)	8 (100)	11 (73)	8 (100)	8 (100)	8 (100)	13 (100)	6 (86)	15 (100)	84 (93)
Anorexia	1 (33)	2 (40)	5 (63)	10 (67)	5 (63)	5 (63)	4 (50)	11 (85)	6 (86)	14 (93)	63 (70)
Fatigue	1 (33)	2 (40)	6 (75)	8 (53)	6 (75)	5 (63)	6 (75)	9 (69)	5 (71)	12 (80)	60 (67)
Hypertension	0 (0)	2 (40)	6 (75)	8 (53)	4 (50)	6 (75)	5 (63)	10 (77)	5 (71)	7 (47)	53 (59)
Dry skin	0 (0)	1 (20)	3 (38)	5 (33)	5 (63)	5 (63)	8 (100)	9 (69)	3 (43)	8 (53)	47 (52)
Nausea	1 (33)	4 (80)	4 (50)	2 (13)	6 (75)	6 (75)	4 (50)	5 (38)	3 (43)	11 (73)	46 (51)
Dysphonia	0 (0)	4 (80)	3 (38)	3 (33)	5 (63)	5 (63)	5 (63)	9 (69)	5 (71)	6 (40)	45 (50)
Decreased weight	2 (67)	2 (40)	5 (63)	4 (27)	4 (50)	4 (50)	3 (38)	5 (38)	4 (57)	10 (67)	43 (48)
Vomiting	1 (33)	2 (40)	4 (50)	4 (27)	5 (63)	3 (38)	3 (38)	6 (46)	4 (57)	9 (60)	41 (46)
Rash	2 (67)	4 (80)	5 (63)	4 (27)	5 (63)	4 (50)	4 (50)	2 (15)	3 (43)	6 (40)	39 (43)
Pruritus	0 (0)	1 (20)	2 (25)	4 (27)	4 (50)	5 (63)	2 (25)	5 (38)	2 (29)	7 (47)	32 (36)
Acne	0 (0)	0 (0)	1 (13)	2 (13)	2 (25)	3 (38)	4 (50)	7 (54)	3 (43)	4 (27)	26 (29)
Cough	0 (0)	0 (0)	2 (25)	4 (27)	3 (38)	4 (50)	3 (38)	4 (31)	2 (29)	3 (20)	25 (28)
Headache	0 (0)	2 (40)	5 (63)	4 (27)	0 (0)	1 (13)	4 (50)	5 (38)	1 (14)	3 (20)	25 (28)
Dysgeusia	0 (0)	1 (20)	1 (13)	1 (7)	4 (50)	3 (38)	1 (13)	4 (31)	3 (43)	5 (33)	23 (26)
Dyspnoea	0 (0)	0 (0)	2 (25)	4 (27)	2 (25)	4 (50)	1 (13)	5 (38)	1 (14)	3 (20)	22 (24)
Myalgia	1 (33)	1 (20)	4 (50)	3 (33)	2 (25)	0 (0)	4 (50)	2 (15)	1 (14)	3 (20)	21 (23)
PPE syndrome	0 (0)	2 (40)	3 (38)	3 (33)	2 (25)	0 (0)	1 (13)	6 (46)	2 (29)	0 (0)	19 (21)
Increased ALT	0 (0)	1 (20)	1 (13)	2 (13)	4 (50)	1 (13)	0 (0)	6 (46)	1 (14)	2 (13)	18 (20)
Dizziness	0 (0)	1 (20)	3 (38)	1 (7)	2 (25)	0 (0)	2 (25)	2 (15)	3 (43)	2 (13)	16 (18)
Nasopharyngitis	1 (33)	0 (0)	0 (0)	4 (27)	2 (25)	0 (0)	3 (38)	2 (15)	1 (14)	3 (20)	16 (18)
Abdominal pain	2 (67)	2 (40)	3 (38)	0 (0)	1 (13)	0 (0)	1 (13)	1 (8)	1 (14)	4 (27)	15 (17)
Increased AST	0 (0)	1 (20)	1 (13)	2 (13)	4 (50)	0 (0)	0 (0)	5 (38)	0 (0)	2 (13)	15 (17)

Study part	A1			B1				
(b)								
Cediranib dose, mg	20	30	45	20	25	30	37.5	45
Gefitinib dose, mg	250	250	250	500	500	500	500	500
Number of patients, *n*	3	5	8	8	8	8	13	7
Any DLT AE[a]	0	1	3	3	5	2	7	4
Diarrhoea[a]	0	0	1	3	3	0	6	1
Fatigue	0	0	0	1	0	2	2	1
Anorexia	0	0	1	1	0	0	3	0
Hypertension	0	1	2	0	0	0	1	1
Acne	0	0	0	0	1	1	1	1
PPE syndrome	0	0	0	1	0	0	2	0
Asthenia	0	0	1	0	0	0	0	1
Malaise	0	0	0	0	0	0	1	0
Rash[a]	0	0	0	0	1	0	0	0

As no dose escalation occurred in parts A2 or B2, no DLTs were defined in these cohorts. Patients with AEs in more than one category are counted once in each of those categories (so may appear more than once in the table).

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; PPE, palmar-plantar erythrodysesthesia syndrome (hand–foot syndrome).

a Criteria for DLT was any AE grade ⩾ 3 not clearly related to disease progression and considered by the investigator to be related to one or both study treatments that occurred within the first 21 days of dosing in patients who were evaluable at the time of the safety review meeting (minimum of 3). For additional information see Section 2.

the 45 mg cohort in part A1 was known to be 38% (not a non-tolerable dose according to protocol criteria), the safety review committee approved a protocol amendment to allow further dose escalation to 37.5 mg and 45 mg in part B1. To accurately characterise the safety profile of cediranib 37.5 mg in combination with gefitinib 500 mg, it was felt necessary to expand this cohort to 13 patients. Both 37.5 mg and 45 mg cohorts were declared tolerable. There were no plans to escalate the dose beyond 45 mg since this was the MTD in the monotherapy study.[10]

In total 10 patients died during the study; none of the deaths were considered by the investigator to be related to study treatment and all were considered to be a result of the patients' underlying disease.

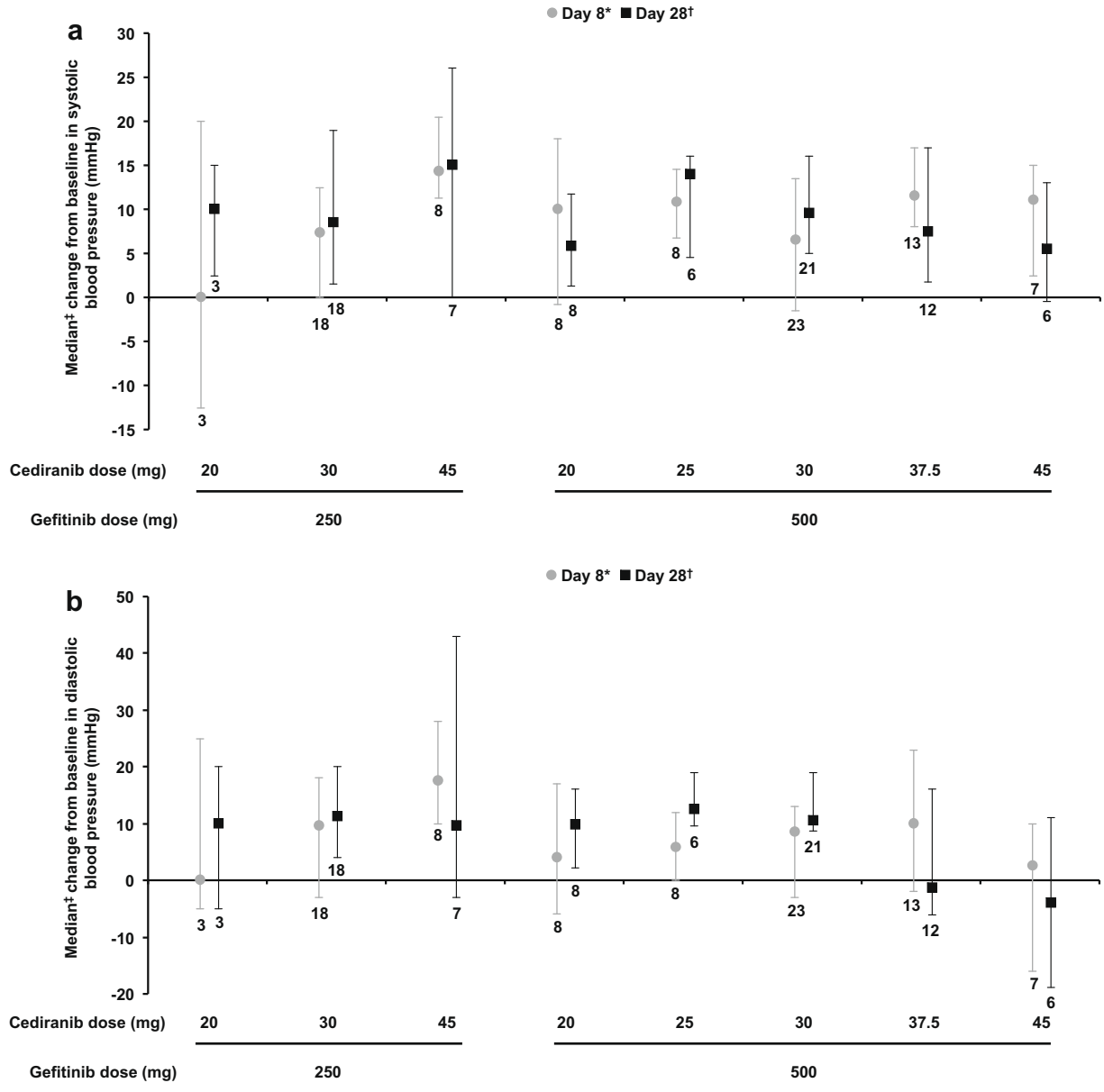
Increases in thyroid-stimulating hormone (TSH) above the normal range (>5 mu/L) were observed in approximately 37% of patients with a baseline and a post-dose reading. All these increases were seen in patients receiving cediranib ⩾30 mg. A minority of these patients developed reductions in free or total thyroxine (T4) to levels below the lower limit of normal;

there was only one reported AE of symptomatic hypothyroidism (CTC grade 2).[17] With the exception of TSH, there were no clinically relevant trends in laboratory parameters and, with the exception of blood pressure, no clinically relevant trends in vital signs, physical findings or ECG observations. The majority of patients experienced early, dose-dependent increases in SBP and DBP during part A; the increases were less marked and were not dose-dependent during part B (Fig. 2).

3.3. *Pharmacokinetics*

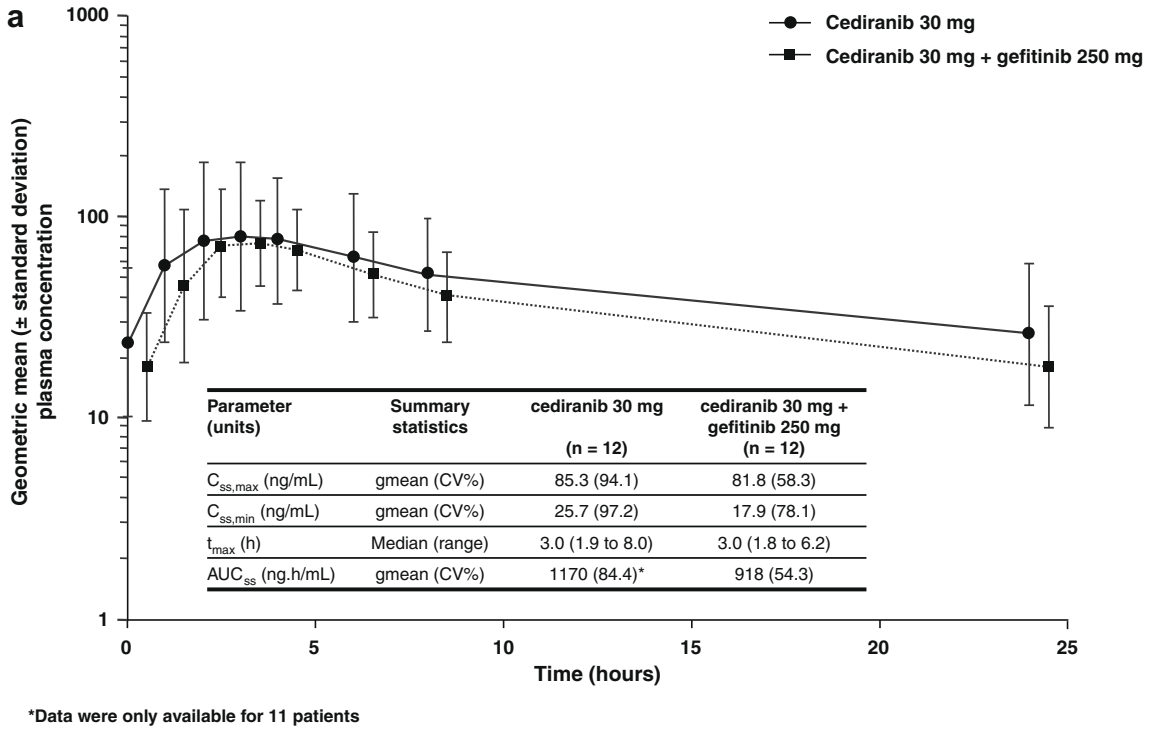
The pharmacokinetic parameters of cediranib and gefitinib were explored in parts A2 and B2 (Fig. 3). In part A2, a 21% reduction in AUC_{ss} was observed for cediranib 30 mg with gefitinib 250 mg for 14 days compared with cediranib 30 mg alone for 7 days. A smaller reduction (8%) in AUC_{ss} in part B2 was observed for cediranib 30 mg with gefitinib 500 mg compared with cediranib 30 mg alone. The results of a pooled analysis of data from parts A and B showed a statistically significant 16% reduction in AUC_{ss} (Table 3). The same pattern was not observed for the $C_{ss,max}$; the $C_{ss,max}$ of cediranib 30 mg was similar when received with gefitinib 250 mg or 500 mg compared with cediranib 30 mg alone (Table 3). The results of a pooled analysis of data from parts A and B showed a 2% reduction in $C_{ss,max}$.

The pharmacokinetic profile of gefitinib 250 or 500 mg with cediranib was similar to that seen previously when gefitinib was administered alone (Table 4).[18,19]



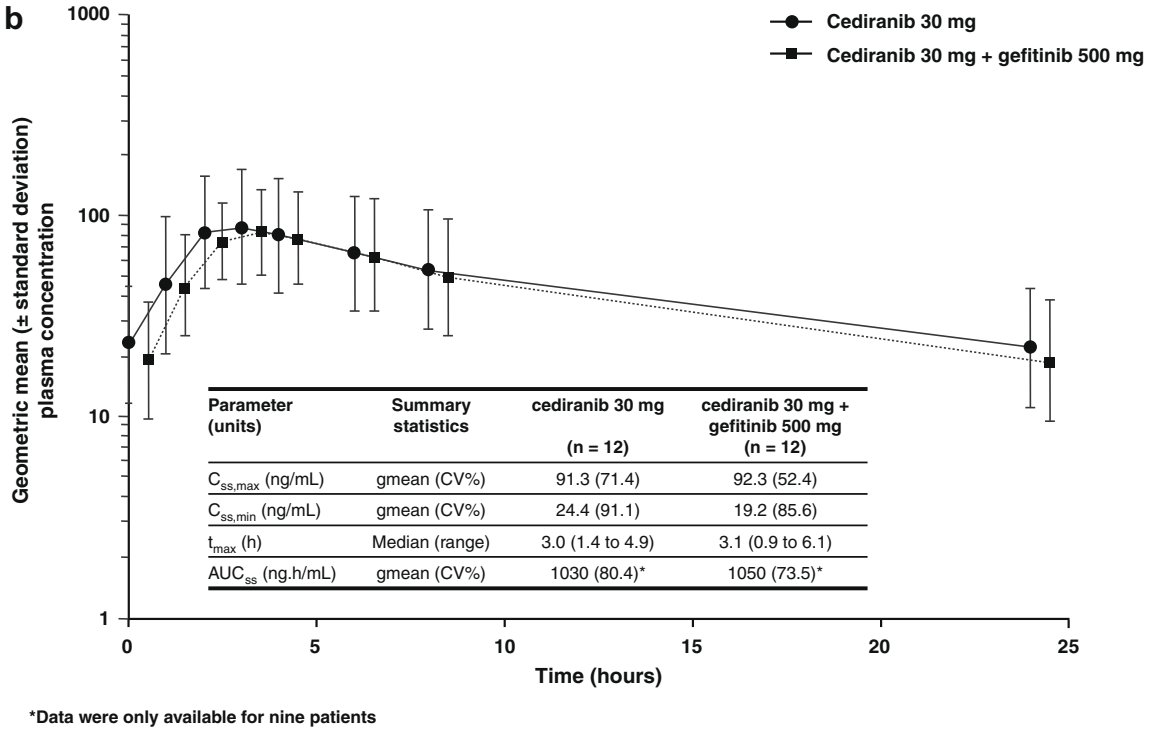
Blood pressure was measured predose
*Day 7 for part A2/B2; †Day 21 for part A2/B2; ‡Error bars represent the first and third quartiles
N numbers are shown below each data point

Fig. 2 – Changes in (a) systolic and (b) diastolic blood pressure on days 8 and 28.



Parameter (units)	Summary statistics	cediranib 30 mg (n = 12)	cediranib 30 mg + gefitinib 250 mg (n = 12)
$C_{ss,max}$ (ng/mL)	gmean (CV%)	85.3 (94.1)	81.8 (58.3)
$C_{ss,min}$ (ng/mL)	gmean (CV%)	25.7 (97.2)	17.9 (78.1)
t_{max} (h)	Median (range)	3.0 (1.9 to 8.0)	3.0 (1.8 to 6.2)
AUC_{ss} (ng.h/mL)	gmean (CV%)	1170 (84.4)*	918 (54.3)

*Data were only available for 11 patients



Parameter (units)	Summary statistics	cediranib 30 mg (n = 12)	cediranib 30 mg + gefitinib 500 mg (n = 12)
$C_{ss,max}$ (ng/mL)	gmean (CV%)	91.3 (71.4)	92.3 (52.4)
$C_{ss,min}$ (ng/mL)	gmean (CV%)	24.4 (91.1)	19.2 (85.6)
t_{max} (h)	Median (range)	3.0 (1.4 to 4.9)	3.1 (0.9 to 6.1)
AUC_{ss} (ng.h/mL)	gmean (CV%)	1030 (80.4)*	1050 (73.5)*

*Data were only available for nine patients

Fig. 3 – Geometric mean (±standard deviation) plasma concentration of cediranib 30 mg on days 7 and 21. Inlaid tables show pharmacokinetic parameters for cediranib. (a) Part A2 and (b) part B2.

3.4. *Efficacy*

Preliminary evidence of antitumour activity was observed with eight patients (9%) achieving a partial response with a median duration of response of 4.2 months (range 1.4–12 months); 6/18 patients with renal cell carcinoma (RCC, 20 mg/500 mg; 25 mg/500 mg; 30 mg/500 mg [$n = 3$]; 37.5 mg/500 mg), 1/14 with lung cancer (mesothelioma; 45 mg/250 mg) and one with osteosarcoma 30 mg/500 mg). In addition, 38 patients experienced stable disease. These included nine patients with a confirmed minor response (10–30% reduction). Fig. 4 shows the best change in target lesion size for each patient. The results are suggestive of a dose response.

Table 3 – Statistical analysis of the effect of gefitinib on the pharmacokinetics of cediranib.

Parameter (units)	Summary statistics	Cediranib 30 mg + gefitinib 250 mg:cediranib 30 mg	Cediranib 30 mg + gefitinib 500 mg:cediranib 30 mg	Cediranib 30 mg + gefitinib 250 or 500 mg:cediranib 30 mg
AUC_{ss} (ng h/ml)	*n*	11	8	19
	Ratio	0.79	0.92	0.84
	(90% CI)	(0.62, 1.00)	(0.74, 1.15)	(0.72, 0.98)
$C_{ss,max}$ (ng/ml)	*n*	12	11	23
	Ratio	0.96	1.01	0.98
	(90% CI)	(0.73, 1.26)	(0.84, 1.21)	(0.84, 1.15)

Ratios of >1 indicate an increase in exposure of cediranib when dosing with gefitinib.
AUC_{ss}, area under plasma concentration–time curve at steady-state; $C_{ss,max}$, maximum plasma drug concentration at steady state; and CI, confidence interval.

Table 4 – Pharmacokinetic parameters for gefitinib.

Parameter (units)	Summary statistics	Cediranib 30 mg + gefitinib 250 mg, *n* = 13	Cediranib 30 mg + gefitinib 500 mg, *n* = 12
$C_{ss,max}$ (ng/ml)	gmean (CV%)	215 (83.2)	634 (71.7)
$C_{ss,min}$ (ng/ml)	gmean (CV%)	112 (107)	305 (114)
t_{max} (h)	Median (range)	4.0 (2.0–8.1)	5.8 (2.0–8.1)
AUC_{ss} (ng h/ml)	gmean (CV%)	3630 (84.8)	9520 (87.8)[a]

AUC_{ss}, 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; and t_{max}, time to reach maximal concentration.
[a] Data were only available for 9 patients.

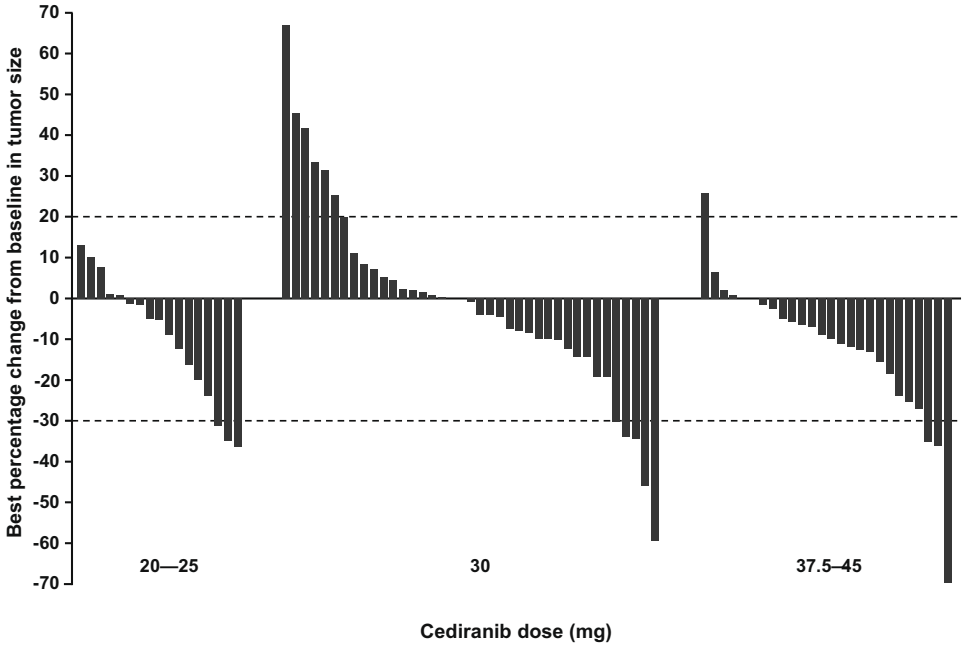


Fig. 4 – Tumour response evaluation. Best change in target lesion size.

3.5. *Pharmacodynamics*

Acute increases in VEGF levels were seen at all cediranib doses (Fig. 5a). Acute increases in bFGF levels were observed in some patients although data were generally inconclusive (Fig. 5b). Reductions in sVEGFR-2 levels were observed following treatment (Fig. 5c). Decreases were seen in sTie-2 levels (Fig. 5d).

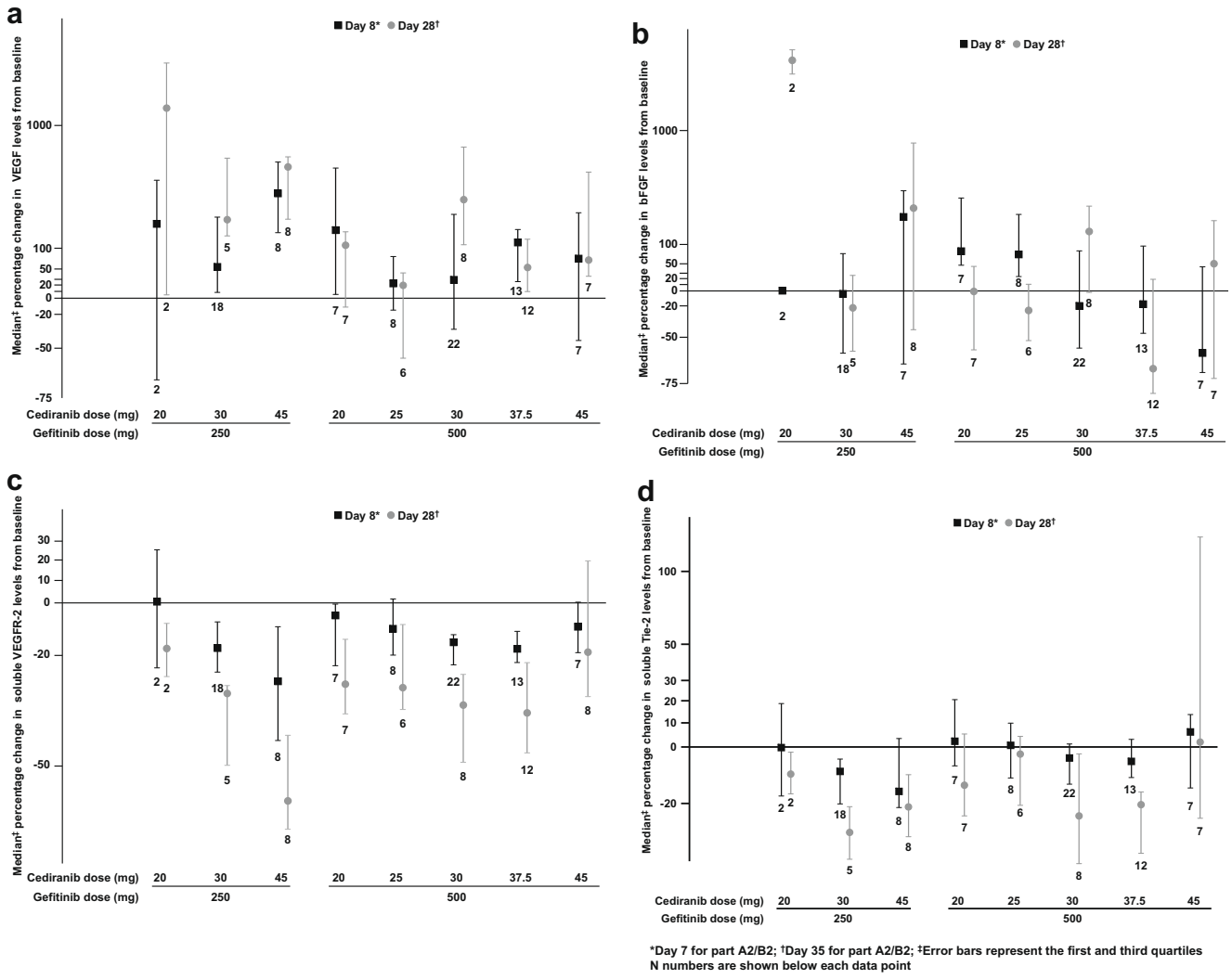


Fig. 5 – Changes in (a) VEGF, (b) bFGF, (c) soluble VEGFR-2 and (d) soluble Tie-2 levels on days 8 and 28. Data are presented on a log scale.

4. Discussion

This is the first clinical evaluation of cediranib in combination with gefitinib. Combination treatment was generally well tolerated with manageable AEs. The protocol-defined MTD of cediranib was 30 mg/day with gefitinib 250 mg/day (part A1). Cediranib 45 mg/day was the maximum dose investigated with gefitinib 500 mg/day (part B1) and was considered to be a tolerated dose, however, as no further doses were investigated it was not possible to formally identify this as the MTD in part B1. The reasons for the different tolerated doses between the two parts of the study are unclear; it could be a result of the caveat regarding diarrhoea in the DLT definition or a chance finding since a low number of DLTs were required to declare a dose intolerable. Alternatively, increased investigator experience of AE management may have played a role.

The most common AEs considered to be related to cediranib were diarrhoea, hypertension, anorexia and fatigue. Diarrhoea, anorexia and fatigue have previously been associated with either agent alone.[10,20] Hypertension is emerging as a class effect of VEGF-signalling inhibitors.[10,21–24] In this study hypertension was generally mild (mostly grades 1 and 2) and manageable. Skin toxicities were also frequently reported, such as dry skin, hand–foot syndrome and acneiform rash. Acneiform rash is most likely to result from EGFR inhibition by gefitinib.[25] Hoarseness has been linked with VEGF-signalling inhibition[26] and was reported by 44 (49%) patients in this study. Increases in TSH were observed, particularly at cediranib 30 mg and above, however, no consistent reductions in total or free T4 were observed. Modulation of the function of the thyroid gland has been associated with certain inhibitors of VEGF signalling[27–30] although the mechanism underlying the association is unclear.

The pharmacokinetic results did not show any increase in exposure to cediranib following the addition of gefitinib. Reductions in AUC_{ss} were observed in both part A2 and part B2 of the study; however, overall reductions in AUC_{ss} in excess of 28% were ruled out. No significant change in $C_{ss,max}$ was observed in either part A2 or part B2. Taking the pharmacokinetic data together, it was concluded that changes seen in cediranib 30 mg steady-state plasma pharmacokinetic parameters, when given for 7 days or in combination with

gefitinib 250 or 500 mg for 14 days, did not appear to be substantial or clinically meaningful.

In this study combination treatment with cediranib and gefitinib showed encouraging antitumour activity with eight patients (9%) achieving a partial response. In addition, 38 patients (42%) had a best response of stable disease, of which nine patients had confirmed reductions of 10–30% on consecutive visits. A recent Phase I study of sorafenib in combination with gefitinib in 31 patients with refractory or recurrent NSCLC patients reported that one patient (3%) achieved a partial response and 20 (65%) experienced stable disease.[31]

The most common primary tumour type was RCC (18 patients). The response rates in this subgroup were of particular interest given the positive efficacy data from two recent Phase III studies of the multitargeted tyrosine kinase inhibitors sorafenib[32] and sunitinib.[33] In the present study six patients (33%) with RCC achieved a partial response with a median response duration of 6 months (range 3.5–12) at the time of the analysis. The antitumour activity may be largely due to the treatment with cediranib since the previous studies of EGFR inhibitors as monotherapy showed poorer response rates.[34–36] Furthermore, recently reported Phase II studies of cediranib in patients with advanced RCC, partial response rates were encouraging.[37]

In early clinical trials, biomarker assays can provide supporting evidence as to whether the drug concentration achieved can inhibit the putative target(s). Consistent with the findings from a previous study of cediranib monotherapy, decreases in sVEGFR-2 levels were observed following treatment.[10] This reduction might reflect a decreased release or production of VEGFR-2 by vascular endothelial cells. Increases in VEGF levels were also observed in this study, consistent with the previous studies of cediranib[10] and other VEGFR tyrosine kinase inhibitors.[38] This increase might partly reflect an increased production of VEGF by tumour cells due to acute stress induced by inhibition of VEGFR tyrosine kinase signalling. However, recent preclinical data suggest that the canonical changes in sVEGFR-2 and VEGF observed with VEGFR tyrosine kinase inhibitors may derive from both tumour-independent and tumour-dependent responses.[39] Decreased tumour perfusion induced by cediranib and gefitinib treatment was established by computed tomography perfusion in subset of patients in this study.[40] The results of the current study show that the combination of cediranib and gefitinib is generally well tolerated with evidence of clinical activity. Further investigation is merited. This combination may be of particular interest in patients with RCC and NSCLC, although it needs to be confirmed whether the combination of cediranib and gefitinib shows more antitumour activity than either single agent. In the context of RCC and NSCLC, it should be noted that combined inhibition of the VEGFR and EGFR signalling pathways with bevacizumab and erlotinib has not produced consistent efficacy results. A Phase II study in patients with metastatic RCC showed that adding erlotinib to bevacizumab did not provide any additional efficacy benefit compared with bevacizumab alone.[41] More recently, the BETA Phase III study in advanced second-line NSCLC demonstrated significant improvements in progression-free survival and objective response rate with bevacizumab plus erlotinib versus erlotinib alone despite failing to achieve the primary objective of longer overall survival with the combination.[42] Cediranib is currently in Phase III development in first-line colorectal cancer and recurrent glioblastoma. Work is ongoing to determine its potential utility in a range of other tumours including lung cancer.

Conflict of interest statement

J. Robertson, O. Saunders and J.M. Jürgensmeier hold AstraZeneca stock and are employees of AstraZeneca. T.A. Puchalski holds AstraZeneca stock and was formerly an employee of AstraZeneca. No other authors have any disclosures.

Acknowledgements

This study, including editorial assistance provided by Dr. Jen Lewis of Mudskipper Bioscience, was supported financially by AstraZeneca.

We would like to thank Ute Zirrgiebel for assessment of soluble biomarkers.

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