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Cediranib monotherapy in patients with advanced renal cell carcinoma: Results of a randomised phase II study ☆

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Abstract *Background:* Cediranib is a highly potent vascular endothelial growth factor (VEGF) signalling inhibitor with activity against VEGF receptors 1, 2 and 3. This Phase II, randomised, double-blind, parallel-group study compared the efficacy of cediranib with placebo in patients with metastatic or recurrent clear cell renal cell carcinoma who had not previously received a VEGF signalling inhibitor.

Methods: Patients were randomised (3:1) to cediranib 45 mg/day or placebo. The primary objective was comparison of change from baseline in tumour size after 12 weeks of therapy. Secondary objectives included response rate and duration, progression-free survival (PFS) and safety and tolerability. Patients in the placebo group could cross over to open-label cediranib at 12 weeks or earlier if their disease had progressed. This study has been completed and is registered with ClinicalTrials.gov, number NCT00423332.

☆ Previous presentations: 2008 International Kidney Cancer Symposium (poster presentation); 2009 joint congress of the European Cancer Organisation and European Society for Medical Oncology (oral presentation); 2009 European Multidisciplinary Meeting on Urological Cancers (oral presentation).

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Findings: Patients ($n = 71$) were randomised to receive cediranib ($n = 53$) or placebo ($n = 18$). The primary study outcome revealed that, after 12 weeks of therapy, there was a significant difference in mean percentage change from baseline in tumour size between the cediranib (–20%) and placebo (+20%) arms ($p < 0.0001$). Eighteen patients (34%) on cediranib achieved a partial response and 25 (47%) experienced stable disease. Cediranib treatment prolonged PFS significantly compared with placebo (hazard ratio (HR) = 0.45, 90% confidence interval: 0.26–0.76, $p = 0.017$; median PFS 12.1 versus 2.8 months). The most common adverse events in patients receiving cediranib were diarrhoea (74%), hypertension (64%), fatigue (58%) and dysphonia (58%).

Interpretation: Cediranib monotherapy demonstrated significant evidence of antitumour activity in patients with advanced renal cell carcinoma. The adverse event profile was consistent with previous studies of cediranib 45 mg.

1. Introduction

In 2010, cancer of the kidney and renal pelvis was estimated to account for approximately 13,000 deaths in the United States alone.[1] Clear-cell renal cell carcinoma (RCC) is the most common form of kidney cancer and is characterised by mutations in the *von Hippel-Lindau* (*VHL*) gene. In normoxic conditions, VHL breaks down hypoxia-inducible factor (HIF); however, when *VHL* is mutated, HIF is not degraded and increased levels result in overexpression of vascular endothelial growth factor (VEGF).[2] Small-molecule tyrosine kinase inhibitors (TKIs) that target the VEGF signalling pathway have been approved as monotherapy for the treatment of RCC.[3]

Cediranib (AZD2171) is a once-daily oral VEGF signalling inhibitor of all three VEGF receptors (VEGFR-1, -2, and -3).[4–6] The IC_{50} for cediranib versus VEGFR-2 in *in vitro* kinase assays is <1 nM, compared with 9 nM (sunitinib),[7] 30 nM (pazopanib)[8] and 90 nM (sorafenib)[9] for VEGFR TKIs approved for the treatment of patients with RCC. Early clinical data demonstrated encouraging antitumour activity across a broad range of tumours, both as monotherapy[6,10–14] and in combination with certain chemotherapy regimens.[15–18] Common adverse events reported with cediranib include hypertension, diarrhoea and fatigue.

This Phase II, randomised, double-blind, parallel-group study (ClinicalTrials.gov identifier NCT00423332; AstraZeneca study code 2171IL0030) compared cediranib with placebo in patients with advanced RCC who had not received previous anti-VEGF therapy.

2. Methods

2.1. Study objectives

The primary objective was to determine the efficacy of cediranib versus placebo by comparing changes from baseline in tumour size after 12 weeks of therapy (or at progression if before 12 weeks). Change in tumour size was considered a more sensitive endpoint than objective tumour response rate to assess efficacy for this type of agent in this disease setting based on previous clinical data.[19] Secondary objectives included assessments of overall best change in tumour size (defined as the smallest post-baseline tumour size), objective response rate and duration, progression-free survival (PFS), safety and tolerability, steady-state pharmacokinetic parameters and angiogenesis biomarkers.

2.2. Patients

Adult patients with histological/cytological confirmation of metastatic or recurrent clear-cell RCC/adenocarcinoma were eligible. Patients were required to have one or more lesions measurable by Response Evaluation Criteria In Solid Tumours (RECIST)[20] and a World Health Organisation (WHO) performance status of 0–2. Brain metastases were permitted if asymptomatic and either did not require corticosteroid treatment or were clinically/radiologically stable for $\geqslant$10 days after discontinuation of steroid treatment. Exclusion criteria included previous VEGF-signalling inhibitor therapy; >1 previous immunotherapy; prior cytotoxic chemotherapy for RCC (except 5-fluorouracil used in combination with immunotherapy). The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and the AstraZeneca policy on Bioethics. Each patient provided written informed consent.

2.3. Randomisation and masking

Treatment was randomised using standard software for the generation of random numbers. In order to achieve balance across this study, the randomisation schedule was stratified by country. Study personnel were blinded to treatment until either the start of open-label treatment at week 13, or at progression if this occurred before week 12.

2.4. Study design

In this double-blind study, patients were randomised 3:1 to cediranib 45 mg/day or placebo (Fig. 1). After

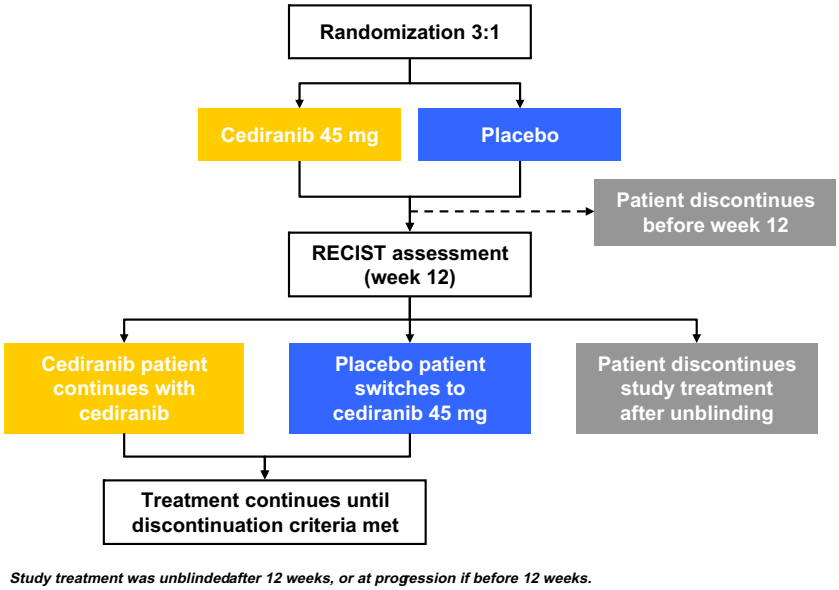

Fig. 1. Study design.

12 weeks (or upon progression if earlier), treatment was unblinded and patients on placebo were given the option of receiving cediranib. Patients on cediranib could continue receiving the compound until progression or withdrawal from study treatment for any reason. The primary analysis took place when all patients had received cediranib/placebo for 12 weeks (or had discontinued from study treatment before 12 weeks).

2.5. Tumour response evaluation

Baseline imaging was performed at screening (up to 14 days before study treatment commenced). Tumour size was evaluated at week 12 and every 8 weeks thereafter and classified according to RECIST 1.0. For patients achieving an unconfirmed complete or partial response, a confirmatory scan was performed $\geqslant$4 weeks after the original scan.

2.6. Pharmacodynamic assessments

Serum and plasma samples for measurement of surrogate markers of angiogenesis and activated endothelial cells were collected pre-dose on day 1, and weeks 4, 8 and 12. VEGF was measured in plasma samples and soluble VEGFR-2 (sVEGFR-2) in serum as described in Drevs et al.[6]

2.7. Safety and tolerability

Assessments of vital signs, laboratory parameters, left ventricular ejection fraction (LVEF; assessed by echocardiogram/MUGA scan) and electrocardiograms (ECGs) were scheduled at baseline and during the treatment period. Adverse events were recorded throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3·0.

2.8. Pharmacokinetics

Blood samples to determine the plasma concentration of cediranib were obtained pre-dose at weeks 4, 8 and 12. Samples were also taken at week 4 to determine the steady-state plasma concentration 1–2 h post-dosing ($C_{ss,1–2\ h}$) and at week 8 to determine the steady-state plasma concentration after 3–4 h post-dosing ($C_{ss,3–4\ h}$).

2.9. Statistical analysis

The primary analysis was performed when all patients had completed $\geqslant$12 weeks of treatment (7th March 2008). The study was designed to have ~80% power to detect a difference of –14% in mean change in tumour size at 12 weeks, at a one-sided significance level of 5% (approximately 65 patients were required). A mean difference of 14% was derived from estimates of maximum tumour size reduction from baseline previously reported for sorafenib and placebo in RCC,[19] with a mean change of –10.1% (sorafenib) and +6.5% (placebo) corresponding to a difference of 16.6%. The study was powered to show superiority of cediranib over placebo, using a one-sided significance level of 5% (equivalent to a two-sided level of 10%). The primary endpoint (change in tumour size after 12 weeks) was calculated using the ratio of week 12 (or on progression if before week 12) tumour size:baseline tumour size, which was log-transformed and analysed using an analysis of covariance (ANCOVA) model, adjusting for baseline tumour size, Memorial Sloan-Kettering Cancer Centre (MSKCC) risk group and centre, and is presented as the % change in tumour size after 12 weeks with two-sided 90% confidence inter-

vals (CIs). As the study design allowed patients on placebo to switch to open-label cediranib after 12 weeks, subsequent analyses were potentially influenced by this.

PFS was defined as the time from randomisation to objective progression (measured by RECIST) or death. PFS was analysed using a log-rank test to calculate a hazard ratio (HR) for the effect of treatment. A 90% CI for the HR was calculated from fitting a Cox proportional-hazards model with treatment as a factor. At the time of the primary analysis, only 28% of events had occurred in the cediranib arm; therefore, an updated analysis was conducted after approximately 1 year of further follow-up (8th March 2009).

The minimum steady-state drug concentration in plasma during the dosing interval ($C_{ss,min}$) was taken as the plasma concentration prior to dosing on weeks 4, 8 and 12. $C_{ss,min}$, $C_{ss,1–2\ h}$ and $C_{ss,3–4\ h}$ were summarised by study day and cediranib dose (received for the 7 days before assessment).

2.10. Role of the funding source

The corresponding author designed the trial in collaboration with the study sponsor. The sponsor provided funding and organisational support, collected the data and undertook the analyses. The corresponding author had unrestricted access to all data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Patients

Between January and November 2007, 105 patients were enrolled and 71 patients were randomised to cediranib ($n = 53$) or placebo ($n = 18$) (Table 1, Fig. 2). The demographic and baseline characteristics were representative of patients with metastatic RCC and were generally well-balanced across the two groups. There were slight numerical imbalances in WHO performance status and MSKCC risk factors and group, which were explored in the efficacy analyses and found not to affect the results. The most common sites of metastatic/locally advanced disease were respiratory sites and lymph nodes. Two (4%) patients randomised to cediranib and two (11%) randomised to placebo had brain/central nervous system metastases at baseline. Of the 18 patients randomised to placebo, 14 went on to receive cediranib after unblinding at week 12 (or progression if before week 12); the remaining four patients discontinued.

3.2. Efficacy

After 12 weeks of therapy, there was a highly statistically significant difference in the primary endpoint of mean percentage change from baseline in tumour size between cediranib (–20%) and placebo (+20%; $p < 0.0001$; Fig. 3A). No tumour size data were available for three patients randomised to cediranib. These patients had progressed and were included in analysis for the primary endpoint at a +20% tumour size increase. The numerical imbalances in WHO performance status and MSKCC risk scores at baseline were accounted for in the prespecified analysis of the primary endpoint (assignment of MSKCC risk factor used WHO performance status along with four other factors). The treatment effect within each MSKCC risk group was also explored and did not yield any substantial trends, supporting the notion that the slight imbalances in WHO performance status and MSKCC risk groups did not

Table 1
Patient characteristics.

Characteristic	Cediranib 45 mg/day ($n = 53$)	Placebo ($n = 18$)
Age group, median (range)	60 (46–75)	61.0 (45–79)
Sex, *n* (%)		
Male	40 (75)	15 (83)
Female	13 (25)	3 (17)
Race, *n* (%)		
Caucasian	52 (98)	18 (100)
Black	1 (2)	0 (–)
WHO performance status, *n* (%)		
0	38 (72)	10 (56)
1	13 (25)	7 (39)
2	2 (4)	1 (6)
Histology type, *n* (%)		
Adenocarcinoma	3 (6)	2 (11)
Clear cell carcinoma	48 (91)	15 (83)
Other	2 (4)	1 (6)
Number of metastatic sites		
0	2 (4)	1 (6)
1	7 (13)	3 (17)
2	19 (36)	7 (39)
3	17 (32)	5 (28)
4	6 (11)	2 (11)
5	2 (4)	0 (–)
Prior therapy, *n* (%)		
Prior chemotherapy (5-FU)	2 (4)	0 (0)
Prior immuno/hormonal therapy	25 (47)	9 (50)
Prior radiotherapy	6 (11)	3 (17)
Prior surgery	49 (92)	16 (89)
Nephrectomy	46 (87)	15 (83)
MSKCC risk group,[a] *n* (%)		
Favourable risk	26 (49)	6 (33)
Intermediate risk	26 (49)	10 (56)
Poor risk	1 (2)	2 (11)

5-FU = 5-fluorouracil. MSKCC = Memorial Sloane-Kettering Cancer Centre. WHO = World Health Organisation.
Due to rounding, not all % values within groups total 100%.
[a] Favourable risk, 0 risk factors; intermediate risk, 1–2 risk factors; poor risk, ⩾3 risk factors. MSKCC risk factors, WHO performance status ⩾2; high (>1.5 × upper limit of reference range) lactate dehydrogenase; high (>2.5 mmol/L) corrected calcium (measured calcium + [0.02 × (40-albumin)]), low (< lower limit of reference range) haemoglobin; absence of nephrectomy.

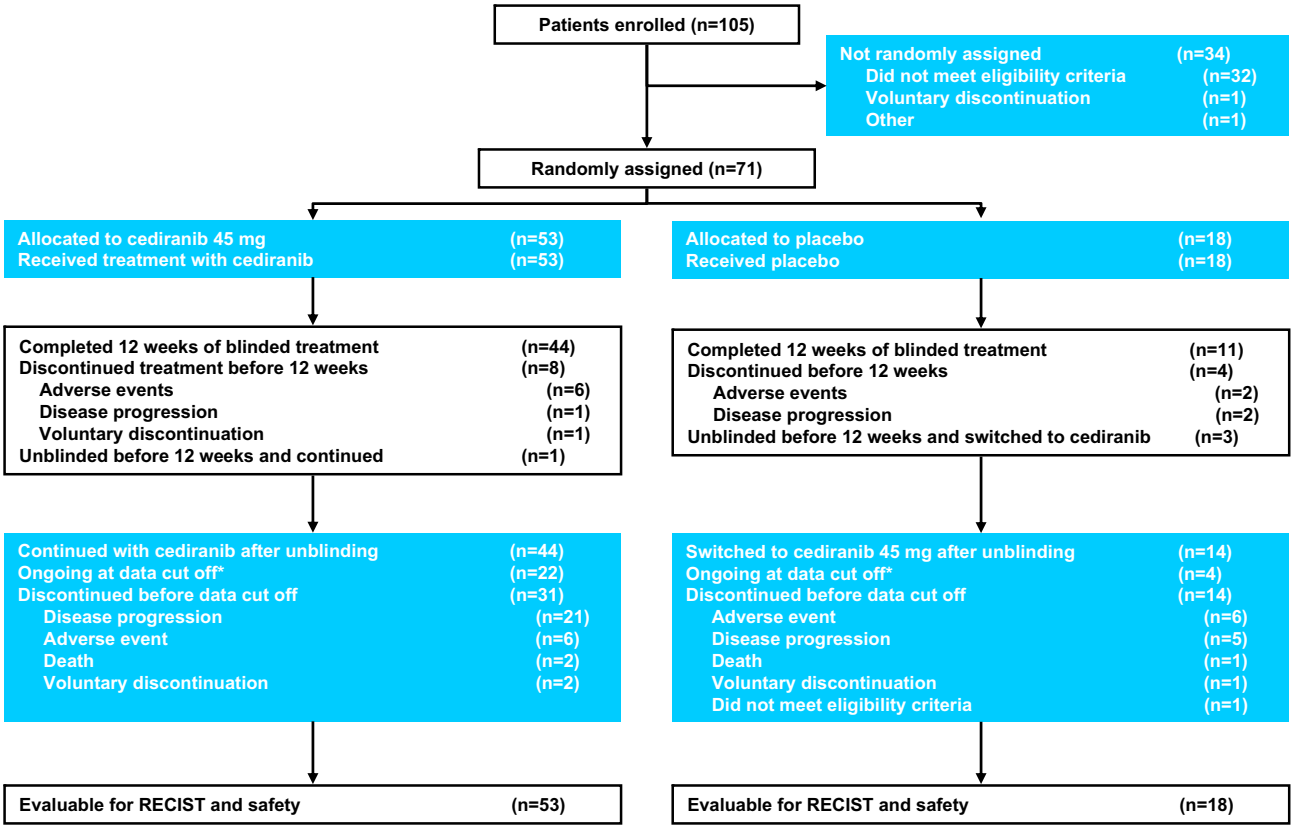

Fig. 2. Patient disposition.

affect the results. Analysis of change from baseline in tumour size at 12 weeks was also performed on the per-protocol population (which excluded patients with a major protocol deviation); the results were consistent with the intent-to-treat population. At the updated analysis, the mean best change in tumour size for patients randomised to cediranib was –31% (Fig. 3B), and the median best change in tumour size was –25%.

Fourteen patients (77.8%) in the placebo arm switched from placebo to cediranib after unblinding at progression or week 12. The geometric mean best percentage change in tumour size while receiving cediranib was –21.6% (Fig. 3B). The majority of these patients ($n = 10$ [71%]) went on to experience a decrease in tumour size while receiving cediranib.

In the cediranib arm, 18 patients (34%) achieved a partial response and 25 (47%) experienced stable disease. Eleven of the 18 responders (61%) had responses lasting for $\geqslant 1$ year. None of the patients who received placebo achieved a partial response during the first 12 weeks of therapy; four patients (22%) experienced stable disease and 13 (72%) showed progressive disease (one patient was non-evaluable as they did not have a RECIST assessment before discontinuation).

At the updated analysis, patients in the cediranib arm showed a significant prolongation in PFS compared with the placebo arm (HR = 0·45 [90% CI: 0.26–0.76]; $p = 0.017$); median PFS was 12.1 versus 2.8 months, respectively (Fig. 4). This analysis was confounded by patients on placebo switching to cediranib before progression and it was likely that the true treatment effect was underestimated. However, the proportion of patients who were progression-free at week 12, which was not influenced by treatment crossover – was estimated (by the Kaplan–Meier method) to be 85% and 28% in the cediranib and placebo arms, respectively.

3.3. Biomarkers

For patients randomised to cediranib, median plasma VEGF levels increased from baseline to the first post-baseline measurement (week 4) and remained elevated at weeks 8 and 12 (Fig. 5A). VEGF levels remained largely unchanged in the placebo arm, however, mean increases were noted in patients receiving placebo at week 8. These were of a smaller magnitude than in patients randomised to cediranib and may have occurred because of the small number of patients and the large variability in these data. Conversely, sVEGFR-2 decreases of approximately 29% after 28 days of study treatment were seen in the cediranib arm (Fig. 5B), while levels in the placebo group remained close to baseline throughout treatment.

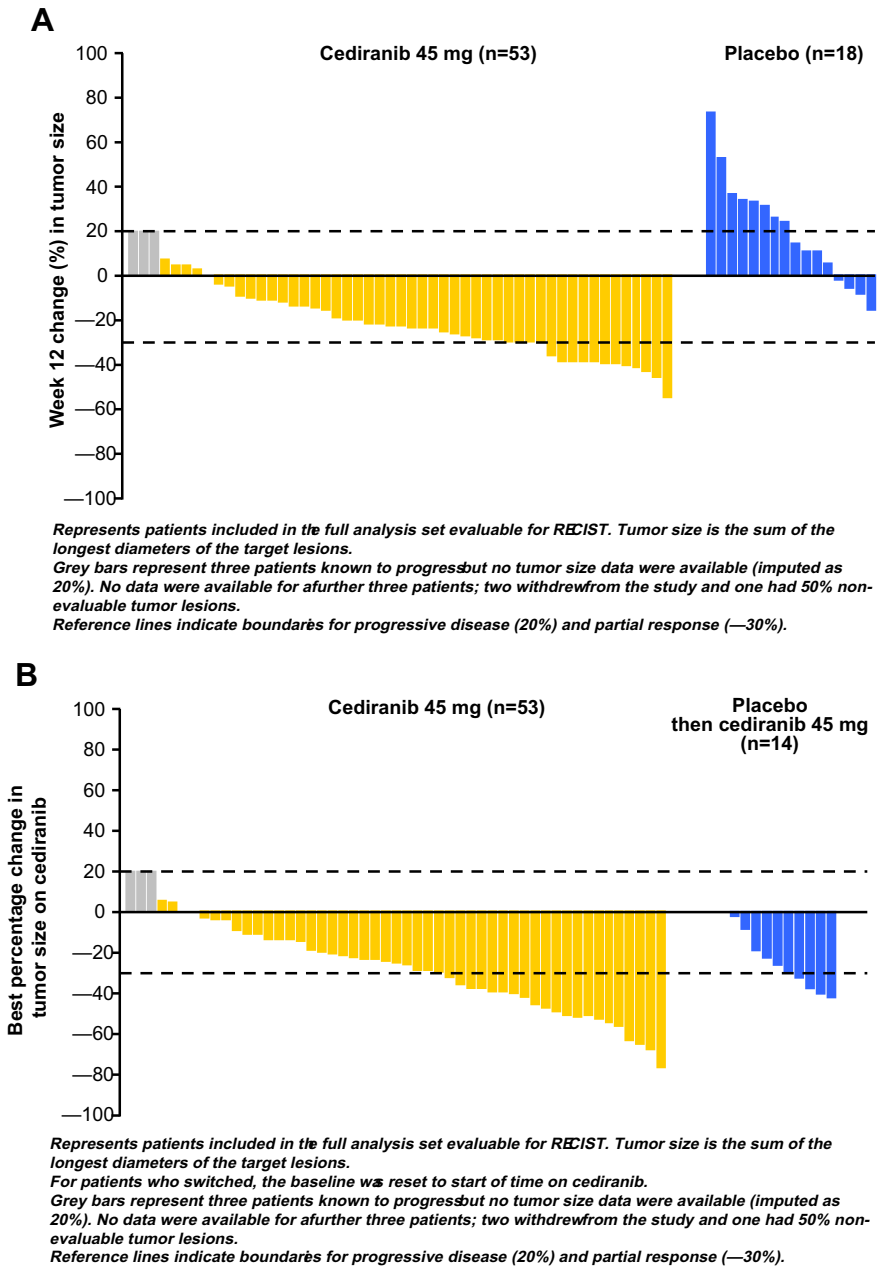

Fig. 3. Efficacy data (A) change in tumour size at week 12 (waterfall plot) and (B) best change in tumour size (waterfall plot).

No notable trends in basic fibroblast growth factor levels were detectable in either arm. No relationship between VEGF or sVEGFR-2 levels and a change in tumour size or best response during the study was observed.

3.4. Safety and tolerability

The mean daily dose of cediranib was approximately 30 mg, with a median overall duration of exposure to cediranib of approximately 1 year. A total of 58/67 (87%) patients receiving cediranib at some point during the study had a dose reduction and/or pause ($n = 50$ dose reduction; $n = 55$ dose pause), with a median time to first reduction/pause of 29 days. Thirty (45%) patients required one dose reduction (to 30 mg), and 18 (27%) required two dose reductions (to 20 mg).

The most common adverse events in patients receiving cediranib were diarrhoea, fatigue, hypertension and dysphonia (Table 2). Overall, 50 patients (75% of those receiving cediranib at any time in the study) experienced a CTCAE grade $\geqslant 3$. The most frequent CTCAEs grade $\geqslant 3$ were hypertension, fatigue and diarrhoea (Table 2).

Serious adverse events were reported in 26 (39%) patients who received cediranib during the study. Serious adverse events reported in >1 patient were abdominal pain, dehydration, diarrhoea, dyspnoea, lower respiratory tract infection and reversible posterior

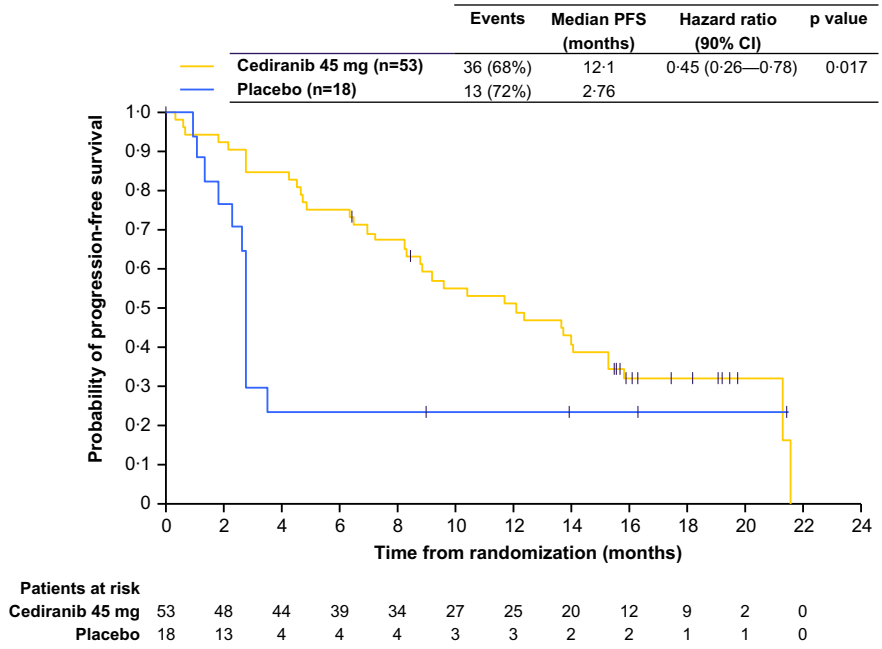

Fig. 4. Progression-free survival.

leukoencephalopathy syndrome (RPLS) (all $n = 2$ [3%]). Three patients (cediranib arm, $n = 1$; placebo arm, $n = 2$) had RPLS. Of the two placebo patients, one received cediranib in error for 7 days before developing RPLS and the other developed RPLS after crossover to cediranib. Overall, 11/67 (16%) patients who received cediranib discontinued treatment due to adverse events. The most common adverse events leading to discontinuation were diarrhoea, fatigue and RPLS (all $n = 2$ [3%]). Six patients had died by the time of the updated analysis (disease progression, $n = 5$; coma, $n = 1$). For the patient who entered a coma, the exact cause of coma or death was not established, but was considered by the investigator to be possibly related to study treatment.

There was a higher incidence of severe (systolic blood pressure [SBP] $\geqslant$180 mmHg or diastolic blood pressure [DBP] $\geqslant$10 mmHg) or moderate (SBP $\geqslant$160 to $<$180 mmHg or DBP $\geqslant$100 to $<$110 mmHg) hypertension in patients who received cediranib (severe, $n = 17$ [32%]; moderate, $n = 24$ [45%]) compared with those who received placebo (severe, $n = 1$ [%]; moderate, $n = 5$ [%]). For the 17 patients on cediranib, the median time to the first event of severe hypertension was 15 days. Hypertension was managed according to the cediranib hypertension management protocol.[13] ECG data did not indicate any safety concern with regard to cediranib. Among the 15 patients receiving cediranib with both baseline and follow-up LVEF data, five had a grade 2 decrease in LVEF (asymptomatic, $<$50–40%), one developed a grade 3 decrease (symptomatic, $<$40–20%) and two had a $>$15% drop in LVEF from baseline. With the exception of one patient, LVEF returned to baseline values while on study treatment.

No clinically significant effect of cediranib on haematological parameters was observed. Most patients on cediranib experienced increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by day 7, but these subsequently stabilized or returned to baseline. There were no increases in bilirubin. Increases in thyroid-stimulating hormone (TSH) were seen in 39 cediranib patients; $>$50% of these patients had values above the upper limit of the reference range. Some patients ($n = 13$ [19%]) with increased TSH had either T3 or T4 below the LLN. No clinically significant changes were observed for other clinical chemistry parameters. Proteinuria occurred in 10 patients on cediranib and two on placebo by day 84 and resulted in one patient discontinuing cediranib treatment.

3.5. Pharmacokinetics

Following administration of cediranib 45 mg, the $C_{ss,min}$ (CV%) geometric means in plasma during the dosing interval on study days 28, 56 and 84 were 41.9 (67.8, $n = 25$), 43.0 (51.9, $n = 20$) and 16.5 (919, $n = 15$) ng/mL, respectively. The $C_{ss,1–2\ h}$ (CV%) geometric mean on study day 28 was 83.0 (70.4, $n = 26$) ng/mL. The $C_{ss,3–4\ h}$ (CV%) geometric mean on study day 56 was 82.2 (45.2, $n = 16$) ng/mL.

4. Discussion

In this randomised Phase II study of patients with metastatic RCC, cediranib monotherapy showed significant evidence of clinical benefit compared with placebo. After 12 weeks of therapy, patients who received cediranib

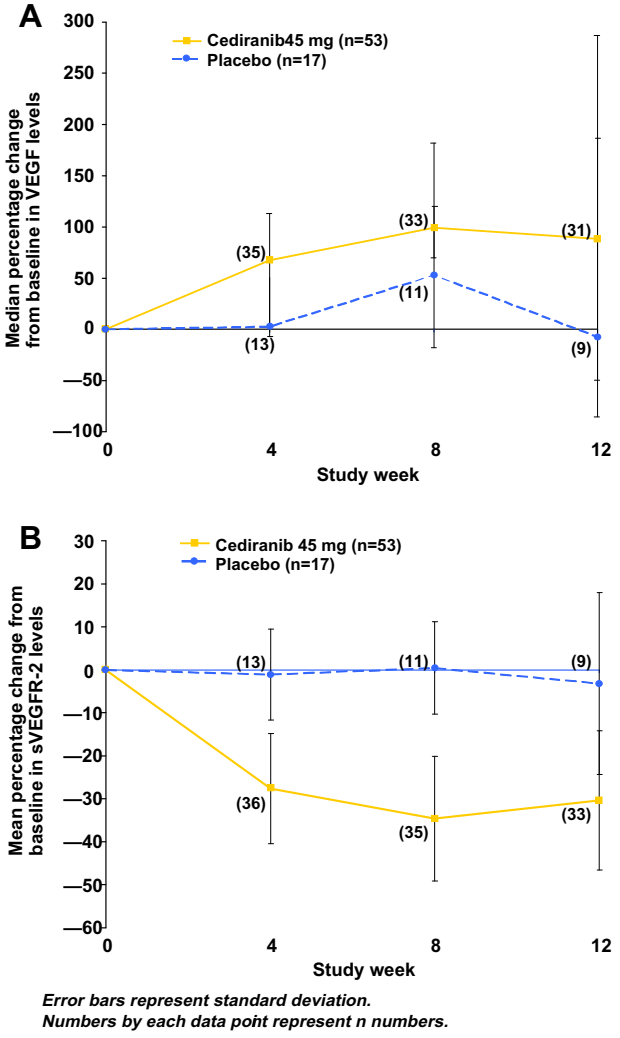

Fig. 5. Changes in biomarker levels over time (A) vascular endothelial growth factor (VEGF) and (B) sVEGFR-2.

45 mg/day showed a statistically significant reduction in tumour size. Over half of the patients on cediranib who achieved a partial response experienced durable responses of at least 1 year. Across the entire study, patients randomised to cediranib had a significant prolongation in PFS compared with placebo. It was likely that the true treatment effect was underestimated because patients in the placebo arm switched to cediranib before progression. The results of an exploratory analysis in which patients in the placebo arm were censored at the time of switching therapy yielded a stronger treatment effect, but this finding should be interpreted with caution because it is likely that these patients would have had the longest times to progression on placebo. Nevertheless, the analysis highlights the impact that the PFS of these four patients has on the HR; the true HR for cediranib versus placebo is unknown. Although cross-study comparisons should be interpreted with caution owing to differences in study design and patient populations, the efficacy results reported here are consistent with those from studies of other VEGF signalling inhibitors in similar patient populations (i.e. patients with advanced RCC, of whom, at least 50% had failed prior immunotherapy). For example, the objective response rate for cediranib in the present study was 34%, which is within the range observed in single-agent assessments of sunitinib (20%),[21] sorafenib (11%),[22] axitinib (44%)[23] and pazopanib (30%).[24] The median PFS reported in these studies for sunitinib, sorafenib and pazopanib was 8.2, 5.5 and 9.2 months, respectively.[21,22,24] In the present study, the median PFS was 12.1 months for cediranib.

It should be noted that limitations of the current phase II study include the imbalance between the treatment groups at baseline for MSKCC score and WHO performance status. Although these numerical imbalances were accounted for in the prespecified ANCOVA analysis of the primary endpoint, the findings should be treated with some caution due to the small patient number.

The adverse event profile in this study was consistent with previous studies of cediranib 45 mg. No new, unexpected toxicities were reported. Adverse events were manageable by supportive care, dose reductions and dose pauses. Based on evidence from this and other studies,[13,14,25,26] the lower dose of 30 mg/day is considered to be the highest chronically tolerated dose of cediranib as monotherapy. The most common adverse events for patients who received cediranib 45 mg in this study were diarrhoea, fatigue, hypertension and dysphonia, and a high proportion of patients (75% of those receiving cediranib at any time in the study) experienced a CTCAE grade $\geqslant 3$; the most frequent CTCAEs grade $\geqslant 3$ were hypertension, fatigue and diarrhoea. These AEs have also been commonly observed in studies of other VEGFR TKIs, including sunitinib, sorafenib, axitinib and pazopanib.[22–24,27] Dysphonia is another class effect associated with TKIs, although the incidence in cediranib-treated patients is somewhat higher than that for sunitinib or sorafenib. RPLS is an adverse event reported with the use of VEGF inhibitors; in the present study, the three patients with RPLS recovered after permanent discontinuation of study treatment and clinical management.

Pharmacokinetic data did not suggest any notable differences in terms of exposure to cediranib between the RCC patient population in this study and previous cediranib studies in patients with other tumour types.[6,10,12]

Consistent with previous cediranib studies, plasma VEGF levels increased following cediranib.[6,18] Median VEGF levels also increased in the placebo arm after 8 weeks, but were of a smaller magnitude than for cediranib; however, data were limited and variable at this timepoint. Increases in VEGF may be a marker for an acute stress response to VEGF signalling inhibition. The observed time-dependent reductions in sVEGFR-2 levels, which may be a surrogate marker for active endothelium or angiogenesis, were similar to those in previous cediranib studies.[6,12,18] Furthermore, the decrease in sVEGFR-

Table 2
Adverse events, *n* (%).

Adverse event	CTC grade	Double-blind period only		Whole study
		Patients randomised to cediranib 45 mg/day ($n = 53$)	Patients randomised to placebo ($n = 18$)	All patients who received cediranib 45 mg/day[a] ($n = 67$)
Common adverse events (all grades; frequency ⩾30%) reported in patients randomised to cediranib				
Diarrhoea		39 (74)	5 (28)	59 (88)
Fatigue		31 (58)	9 (50)	44 (66)
Hypertension		34 (64)	4 (22)	41 (61)
Dysphonia		31 (58)	1 (6)	42 (63)
Nausea		17 (32)	5 (28)	33 (49)
Headache		24 (45)	4 (22)	31 (46)
Constipation		16 (30)	4 (22)	27 (40)
Stomatitis		16 (30)	2 (11)	23 (34)
Adverse events of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grade ⩾3 occurring in more than one patient				
Hypertension	3	10 (19)	0 (–)	13 (19)
Fatigue	3	9 (17)	1 (6)	12 (18)
	4	1 (2)	0 (–)	1 (1)
Diarrhoea	3	4 (8)	0 (–)	9 (13)
Dyspnoea	3	0 (–)	0 (–)	4 (6)
Headache	3	2 (4)	0 (–)	4 (6)
Pain in extremity	3	0 (–)	0 (–)	3 (4)
Back pain	3	2 (4)	0 (–)	3 (4)
Proteinuria	3	0 (–)	0 (–)	3 (4)
Abdominal pain	3	0 (–)	0 (–)	2 (3)
Anorexia	3	0 (–)	0 (–)	2 (3)
Dehydration	3	0 (–)	0 (–)	2 (3)
Hand-foot syndrome	3	0 (–)	0 (–)	2 (3)
Lethargy	3	0 (–)	0 (–)	2 (3)
Lower RTI	3	0 (–)	0 (–)	2 (3)
Nausea	3	0 (–)	0 (–)	2 (3)
Confusional state	3	0 (–)	0 (–)	2 (3)
Myopathy	3	0 (–)	0 (–)	2 (3)
RPLS[b]	3	1 (2)	0 (–)	1 (1)
	4	0 (–)	1 (6)	1 (1)
Stomatitis	3	0 (–)	0 (–)	2 (3)

RTI = respiratory tract infection. RPLS = reversible posterior leukoencephalopathy syndrome.

[a] Includes patients initially randomised to cediranib and those who switched to cediranib from placebo after unblinding (for these patients only adverse events occurring whilst on cediranib were counted).

[b] During the first 12 weeks, one additional patient on the placebo arm also received cediranib for 7 days in error before an adverse event of RPLS.

2 observed here (~29%) is comparable to dose-dependent decreases observed in previous cediranib monotherapy studies. In the placebo arm, sVEGFR-2 levels remained close to baseline levels throughout the study. These trends in biomarker levels are generally consistent with results from studies with other VEGF signalling inhibitors in RCC.[21,28,29]

In conclusion, cediranib monotherapy demonstrated clinical activity in patients with RCC with an acceptable adverse event profile

5. Research in context

5.1. Systematic review

Literature searches were performed using PubMed and international oncology congress databases to identify publications and abstracts reporting clinical trials with VEGFR TKIs in patients with advanced RCC. The search findings were evaluated, and well-designed Phase II/III clinical studies were selected to enable a comparison of the effects of VEGFR TKIs on efficacy and safety outcomes.

5.2. Interpretation

Prognosis is poor for patients with metastatic RCC. Despite advances in recent years, treatment rarely results in a cure, and duration of response is limited. New therapies targeting the VEGFR tyrosine kinase have shown benefit in this patient population, but there remains a need for new agents that optimise inhibition of VEGF signalling. Cediranib is a once-daily, oral VEGFR inhibitor, with activity against all three VEGFRs (-1, -2, and -3) and

has demonstrated encouraging antitumour activity in early clinical studies across a broad range of tumours, both as monotherapy and in combination with certain chemotherapy regimens. Based on these findings, and existing evidence from studies with other VEGFR inhibitors, it was considered appropriate to perform a Phase II, randomised, double-blind, parallel-group study of cediranib in patients with advanced RCC. In this study, once-daily cediranib showed a significant reduction in tumour size compared with placebo, along with a manageable adverse event profile. In addition, more than half of patients who achieved a partial response with cediranib experienced responses lasting $\geqslant 1$ year. When compared with findings from previous studies in advanced RCC, cediranib was shown to provide similar clinical benefits to monotherapy with other VEGFR inhibitors. Therefore, the current randomised Phase II study adds to the existing evidence that VEGFR inhibitors are effective in advanced RCC, with cediranib demonstrating a durable effect in some patients.

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Conflict of interest

R.H. has an immediate family member who owns stock in AstraZeneca. E.P. received fees for consultancy from Novartis and GSK; honoraria from Pfizer and Novartis; and research funding from Pfizer. M.E.G. received fees for consultancy from AstraZeneca. J.M.J. and L.P. are AstraZeneca employees. B.M. was an AstraZeneca employee during the trial and the development of the manuscript. All other authors declared no conflicts of interest.

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