AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00030
Edition Number	1
Date	13 October 2009

A Phase II, Randomised, Double-blind, Parallel-Group Study to Assess the Efficacy of Cediranib (AZD2171, RECENTIN™) 45 mg Versus Placebo following 12 Weeks of Treatment in Patients with Metastatic or Recurrent Renal Cell Carcinoma who have had no Previous Anti-VEGF Therapy

Study dates: First patient enrolled: 2 January 2007
Last patient enrolled: 30 November 2007

Phase of development: Therapeutic exploratory (II)

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

Study centres

This study was conducted at 3 centres in the Netherlands and 5 in the UK.

Publications

Mulders P, Hawkins R, Nathan P, de Jong I, Mookerjee B, Osanto S, et al. Cediranib (RECENTIN™) in patients with advanced renal cell carcinoma: results of a randomized Phase II study. 7th International Kidney Cancer Symposium 2008: abstract 21.

Study design and objectives

Randomised, double-blind, parallel-group study to assess the efficacy of cediranib in patients with metastatic or recurrent renal cell carcinoma (RCC). Patients were randomised 3:1 to receive cediranib 45 mg or placebo. After 12 weeks of blinded, randomised treatment, a Response Evaluation Criteria in Solid Tumours (RECIST) assessment was performed.

Table S1 Primary and secondary objectives and outcome variables

Objective	Outcome variables
Primary	**Primary**
Determine the efficacy of cediranib compared to the efficacy of placebo in patients with metastatic or recurrent renal cell carcinoma (RCC) by comparing changes in tumour size after 12 weeks of therapy (or upon progression if this occurred before 12 weeks).	Change in tumour size at 12 weeks.
Secondary	**Secondary**
To determine the efficacy of cediranib compared to the efficacy of placebo by assessment of RECIST data in patients with metastatic or recurrent RCC.	Absolute and change from baseline in tumour size by visit[a]; best change in tumour size during study [a]; response rate at 12 weeks; best objective tumour response; duration of response [a]; progression-free survival.
To determine the steady-state pharmacokinetic parameters of cediranib in patients with metastatic or recurrent RCC.	Minimum (trough) steady state drug concentration in plasma during dosing interval ($C_{ss,min}$); steady-state plasma concentration after 1 to 2 h post-dosing ($C_{ss,1-2h}$); steady-state plasma concentration after 3 to 4 h post-dosing ($C_{ss,3-4h}$). [b]
To determine the safety and tolerability of cediranib in patients with metastatic or recurrent RCC.	AEs, clinical chemistry, haematology, urinalysis, blood pressure, vital signs, physical examination, ECG, echocardiogram/Multiple Gated Acquisition Scan.
To assess the effect of cediranib on angiogenesis biomarkers.	Biomarker levels and changes from baseline in soluble biomarkers of angiogenesis (VEGF, sVEGFR2, bFGF).

[a] These variables were not specified in the protocol, but were considered appropriate to summarise in this study.
[b] The pharmacokinetic parameters are reported in the main study report.

Target patient population and sample size

Males or females aged ≥18 years with histologically or cytologically confirmed metastatic or recurrent renal cell clear cell/adenocarcinoma; WHO performance status ≤2; ≥1 measurable lesion according to RECIST guidelines. Patients were not to have received prior anti-VEGF

therapy or prior cytotoxic chemotherapy intended to treat their RCC, and were not to have had >1 previous immunotherapy.

With 45 patients on cediranib and 15 on placebo, there was approximately 80% power to detect a difference of –14% in estimated mean % changes in tumour size (cediranib - placebo) at a 1-sided significance level of 5%. Total sample size was approximately 65 patients, allowing for drop-outs.

Investigational product and placebo: dosage, mode of administration, batch numbers

Cediranib (AZD2171) 45 mg was administered as a 30-mg tablet and a 15-mg tablet combination. Cediranib and matching placebo tablets were to be taken orally once daily, no less than 1 h before, or more than 2 h after a meal. Dose reductions were permitted, for management of toxicity. Batch numbers for cediranib and placebo tablets are provided in the main study report.

Duration of treatment

Patients continued with blinded, randomised treatment until the results of the RECIST assessments at 12 weeks were available, at which point their treatment allocation was unblinded. Patients who had not progressed whilst on cediranib then had the option of continuing to receive cediranib (until they met a discontinuation criterion), if considered appropriate by the investigator. There was no break in treatment at the point of unblinding. Patients with disease progression confirmed by RECIST before Week 12 were to be unblinded. Patients who were randomised to placebo then had the option of receiving cediranib, if considered appropriate by the investigator.

Statistical methods

The primary variable was assessed as % change from baseline tumour size at 12 weeks for each patient. The effect of cediranib on change in tumour size was estimated from an analysis of covariance (ANCOVA) model including terms for centre, treatment (cediranib or placebo) and Memorial Sloan-Kettering Cancer Centre (MSKCC) risk group, as well as a covariate for baseline tumour size. All other analyses were exploratory, since unblinding after 12 weeks and potential switching of treatment for patients randomised to placebo meant that from the point of unblinding onwards, all efficacy analyses that used data beyond Week 12 were potentially influenced by the unblinding and switching. The aim of the exploratory analyses was to support the primary variable.

Data cut-off for analyses relating to the double-blind period was on 7 March 2008. There was a 2nd data cut-off on 8 March 2009, to allow reporting of longer-term safety and efficacy data. The ‘double-blind period’ refers to the period of the study for each patient in which they remained blinded to their original randomised study medication. For many patients, this was their first 12 weeks of therapy, but for patients who progressed before Week 12, this period ended once they were unblinded due to this progression.

Subject population

105 patients were enrolled, of which 71 were randomised. Of the 53 patients randomised to cediranib, 44 continued to receive cediranib after unblinding, and 22 were ongoing at the time of the 2nd data cut-off. Of the 18 patients randomised to placebo, 14 switched to cediranib after unblinding, and 4 were ongoing at the time of the 2nd data cut-off.

The demographic and baseline characteristics indicate that the study population was representative of patients with metastatic or recurrent RCC. The randomised treatment arms were generally well balanced with respect to demographic and baseline characteristics. There were numerical imbalances in WHO performance status and MSKCC risk factors, but these were explored by including MSKCC as a factor in the analyses. The number and nature of the major eligibility criteria and post-entry protocol deviations did not raise any concerns about study conduct or quality.

Summary of efficacy results

Primary variable:

There was evidence of anti-tumour activity at 12 weeks: Patients randomised to cediranib had an average decrease in tumour size from baseline of 20.5% and those randomised to placebo had an average increase of 19.5%. The treatment effect (ratio of glsmeans, cediranib:placebo) for change from baseline in tumour size at 12 weeks was statistically significant. The effect indicated that patients on cediranib had on average 33.5% greater decrease in their change from baseline in tumour size than those on placebo.

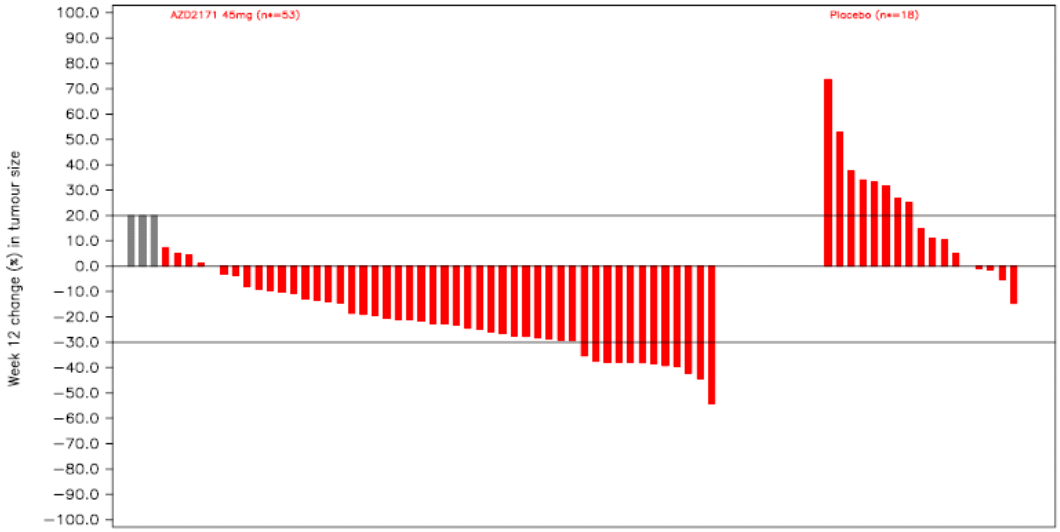
Table S2 Statistical analysis of change from baseline in tumour size at Week 12 (ITT-evaluable for RECIST)

Variable	Treatment	N[a]	N[b]	Adjusted glsmeans	90% CI	Ratio of glsmeans (cediranib-placebo)[d]	90% CI for ratio of glsmeans	P-value
% change in tumour size at Week 12 [c]	Cediranib 45 mg	53	51	-20.48	(-27.2, -13.2)	-33.5	(-40.0, -26.3)	<0.0001
	Placebo	18	17	19.52	(7.7, 32.6)			

[a] Number in ITT evaluable for RECIST set.
[b] Number in ITT evaluable for RECIST set with Week 12 (or progression) tumour size data.
[c] Tumour size = sum of longest diameters of the target lesions. If progression was before Week 12, tumour size at progression was used. Change in tumour size was assessed using baseline scaled ratio (BSR): Week 12 tumour size/baseline tumour size.
[d] ANCOVA performed on log BSRs, exponentiated after analysis to give ratios and presented as % change for ease of interpretation, 100*(ratio –1) = % change from baseline (ie, treatment effect ratio = 0.795 / 1.195 = 0.67 → -33.47%).
Glsmean Geometric least squares mean (adjusted for baseline tumour size, centre, and MSKCC risk group).

At Week 12, 43/53 (81%) patients randomised to cediranib showed some decrease in tumour size compared with 4/18 (22%) patients randomised to placebo (Figure S1).

Figure S1 Week 12 change (%) from baseline in tumour size for each patient (Full analysis set [ITT]-evaluable for RECIST)



* Represents patients in Full Analysis Set (ITT) – evaluable for RECIST, not necessarily the number of patients with change from baseline tumour size data.
Tumour size is the sum of the longest diameters of the target lesions.
If progression was before Week 12, tumour size at progression was used instead of Week 12 tumour size.
Grey bars represent patients known to progress but with missing target lesion data. The change was imputed as +20%.
Reference lines indicate partial response and progressive disease.

Change from baseline in tumour size at 12 weeks was explored for MSKCC risk group, tumour size at baseline, baseline LDH, and baseline VEGF. The difference between cediranib and placebo in % change in tumour size at 12 weeks was consistent in all of these subgroups.

Secondary efficacy variables:

At 12 weeks, 11/53 (20.8%) patients randomised to cediranib had partial response vs none on placebo, 32 (60.4%) patients on cediranib vs 4 (22.2%) on placebo had stable disease, and 8 (15.1%) on cediranib vs 13 (72.2%) had progressed. Tumour responses would be unconfirmed at this stage, as this was the first post-baseline RECIST assessment unless a patient had an assessment to confirm suspected progression.

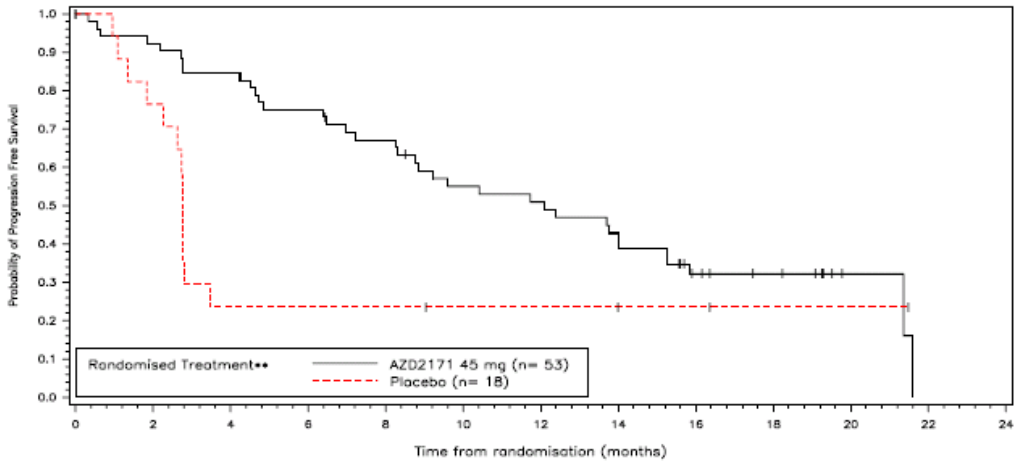
Best objective response during the study, for patients originally randomised to cediranib was as follows: 18/53 (34%) patients had partial response, 25 (47.2%) had stable disease, 9 (17%) had disease progression, and 1 had a response of non-evaluable. Twelve of the 18 responses were ongoing at the time of the 2nd data cut-off; 14 (78%) patients with partial response had responses lasting ≥10 months, and 11 (61%) had responses lasting for ≥1 year.

Geometric mean best change in tumour size during the study was –30.9% for patients who were randomised to cediranib. The data also showed evidence of anti-tumour activity for cediranib in patients who switched to cediranib, including those who had progressed while on

placebo. For patients who switched, best change in tumour size whilst receiving cediranib showed all 14 patients either had a decrease or no change, and 5 reached the target lesion criteria for PR (-30%). Geometric mean best change in tumour size for these patients was -21.6%.

49 (69%) PFS events had occurred by the 2nd data cut-off and the proportions of patients who had progressed were similar in each treatment arm (68% in cediranib vs 72% in placebo). The cediranib arm showed significant prolongation in PFS vs placebo (HR=0.45 [90% CI 0.26, 0.76], p=0.017); median PFS 12.1 months (cediranib) vs 2.8 months (placebo). However, this was confounded by patients on placebo switching to cediranib prior to progression. An exploratory analysis censoring patients who received a different therapy to their randomised treatment prior to progression at the time of switching treatment yielded a HR of 0.14 (90% CI 0.06, 0.30; p<0.0001).

Figure S2 Kaplan-Meier comparison of PFS between cediranib and placebo, extending to last censor time (Full Analysis Set [ITT])



Number of patients at risk*

Month	0	2	4	6	8	10	12	14	16	18	20	22
AZD2171 45mg	53	48	44	39	34	27	25	20	12	9	2	0
Placebo	18	13	4	4	4	3	3	2	2	1	1	0

* The number of patients at risk denotes the number of patients progression free at the beginning of the period.
** Note – 4 of the placebo patients had switched to AZD2171 after unblinding without progressing on placebo

Summary of pharmacodynamic results

There was an initial increase in mean VEGF levels on cediranib, and the level remained above baseline. An increase was also seen in the placebo arm, but this was of a smaller magnitude than for cediranib, and most notably at Day 56: but this may be because of the small number of patients in the placebo arm and large variability in the data. Time-dependent decreases in mean sVEGFR-2 were seen for the cediranib arm; values for the placebo arm remained close to baseline at all time points. Levels of bFGF over time were difficult to interpret owing to the variability in the data and the smaller number of patients with data for that parameter.

Summary of safety

Exposure: Average duration of exposure to cediranib during the whole study was approximately 1 year, and mean daily dose was approximately 30 mg. Median time to first dose reduction or pause in the cediranib arm was 29 days. Of the 67 patients who received cediranib during the whole study, 50 (74.6%) had a dose reduction; 58 (86.6%) had a dose reduction or pause.

AEs: Most common AEs on cediranib in the double-blind period were diarrhoea (39/53 [73.6%] patients), hypertension (34/53 [64.2%]), fatigue (31/53 [58.5%]), and dysphonia (31/53 [58.5%]). These were also the most common AEs in the whole study. The most common AE on placebo was fatigue (9/18 [50%] patients). Although the incidence of fatigue was similar between cediranib and placebo, there were more reports of fatigue ≥grade 3 on cediranib: 10/53 (18.9%) patients on cediranib vs 1/18 (5.6%) on placebo. AEs ≥grade 3 were reported by 31/53 (58.5%) patients on cediranib vs 6/18 (33.3%) on placebo in the double-blind period. Over the whole study, 50/67 (74.6%) patients on cediranib had AEs ≥grade 3.

Six deaths were reported during study treatment or up to 30 days after last dose of study treatment. One patient on cediranib had an AE with outcome of death (coma); for the other 5 patients, the primary cause of death was related to their RCC.

SAEs were reported for 10/53 (18.9%) patients on cediranib vs 3/18 (16.7%) on placebo in the double-blind period. Over the whole study, 26/67 (38.8%) patients on cediranib had an SAE. AEs leading to permanent discontinuation from treatment (DAEs) were reported for 7/53 (13.2%) patients on cediranib vs 4/18 (22.2%) on placebo in the double-blind period. Over the whole study, 11/67 (16.4%) patients on cediranib had a DAE. Three patients had a SAE of reversible posterior leukoencephalopathy syndrome during the study; all 3 patients had received cediranib prior to the event, all 3 cases led to permanent discontinuation, and all subsequently resolved.

Clinical laboratory data: Some patients on cediranib had platelets values below the lower limit of normal, though most were within normal limits. Most patients on cediranib had increased ALT and AST from baseline; 4 patients had ALT ≥ULN, and 2 patients had ALT >5xULN; however, the patients with high transaminases had normal bilirubin. Increased TSH was seen for almost all patients on cediranib, and >50% of these patients had values >ULRR. No clinically significant changes were observed for other haematology or clinical chemistry parameters. The incidence of proteinuria was similar to that seen in other cediranib studies.

Vital signs, ECG, and cardiac monitoring: On cediranib, average BP increased from baseline to Day 7 and subsequently stabilised, as seen in previous studies. No notable changes in average BP on placebo. There was a higher incidence of moderate and severe hypertension based on BP values, for patients on cediranib (17/53 [32%] had severe, 24/53 [45%] had moderate hypertension) compared with placebo (1/18 [5.6%] had severe, 5/18 (28%] had moderate hypertension). Median time to first event of severe hypertension (for patients with worst hypertensive status of severe) on cediranib was 15 days. Median time to first anti-hypertensive medication or increase in dose of baseline anti-hypertensive was 14 days. There

were no clinically important findings for ECG. Cardiac monitoring for left ventricular dysfunction showed that 1/15 evaluable patients on cediranib had a grade 3 decrease in LVEF, and 2 of the 15 patients had a drop >15% from baseline. For all but 1 of the patients with grade 2 reduction in LVEF, their LVEF returned to baseline values whilst on continued study treatment (the 1 patient with a grade 2 reduction that did not return to the baseline value had grade 1 left ventricular dysfunction at baseline).