AstraZeneca

Abbreviated Clinical Study Report Synopsis

Drug Substance	AZD2171 (cediranib)
Study Code	D8480C00038
Edition Number	1
Date	23 March 2010

A Phase II, Randomised, Factorial, Double-blind Study to Investigate the Management of AZD2171 (RECENTIN™, cediranib)-induced Hypertension and Efficacy of cediranib at Doses of 30 mg and 45 mg in Patients with Advanced Solid Tumours

Study dates:

First patient enrolled: 29 November 2005
Last patient enrolled: 20 October 2006
Primary Analysis data cut-off: 26 January 2007
Current data cut-off: 2 September 2009

Phase of development:

Therapeutic exploratory (II)

This abbreviated Clinical Study Report (CSR) synopsis presents data from the whole study. The previous full CSR reported data collected until 26 January 2007. For the current abbreviated CSR, the data cut-off is 2 September 2009.
This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

This study was conducted in 9 centres from 3 countries in Europe: Germany (4), The Netherlands (4) and the United Kingdom (1).

Publications

Langenberg MHG, van Herpen CML, De Bono J, Schellens JHM, Unger C, Hoekman K et al. Effective Strategies for Management of Hypertension After Vascular Endothelial Growth Factor Signaling Inhibition Therapy: Results From a Phase II Randomized, Factorial, Double-Blind Study of Cediranib in Patients With Advanced Solid Tumors. Journal of Clinical Oncology, Vol 27, No 36 (December 20), 2009: pp. 6152-6159.

Langenberg MHG, van Herpen CML, De Bono J, Unger C, Schellens JHM, Hoekman K et al. Optimal management of emergent hypertension during treatment with a VEGF signaling inhibitor: a randomized Phase II study of cediranib. Poster ASCO May/June 2008.

Objectives and criteria for evaluation

A Clinical Study Report (CSR) synopsis was prepared for this study based on an analysis data cut-off of 26 January 2007. The original synopsis presented data from the primary analysis after all patients had completed the first 12 weeks of treatment. This report presents updated data from all patients up to a data cut-off of 2 September 2009. One patient was receiving treatment in the study at the time of the current data cut-off. The aim of this report is to assess all data in the entire study period to confirm if the conclusions from the primary analysis remain unchanged, and if there are any differences to explore them in light of the long term safety and efficacy data collected. In addition, this report provides supplementary text to the original reporting of the pharmacokinetic (PK) and pharmacokinetic/ pharmacodynamic (PK/PD) secondary objectives, for the purpose of clarification. The objectives covered in this report are summarised below.

Table S1 Study objectives and outcome variables relevant to this report

Objectives	Outcome variables
Secondary	**Secondary**
To estimate the activity of cediranib monotherapy using objective response rate (ORR) (consisting of complete response [CR] and partial response [PR]) and stable disease rate based on Response Evaluation Criteria in Solid Tumours (RECIST), changes in tumour size and serological markers (where appropriate).	ORR (consisting of CR + PR) and stable disease rate according to RECIST. Duration of response.[a] Changes in tumour size.
To determine the steady-state pharmacokinetic (PK) parameters of cediranib.	Day 14: Area under the plasma concentration time curve at steady-state (AUC_{ss}); Maximum (peak) steady-state drug concentration in plasma ($C_{ss,max}$); Minimum (trough) steady-state drug concentration in plasma ($C_{ss,min}$); Time to reach peak or max concentration or max response following drug administration (t_{max}).

Table S1 Study objectives and outcome variables relevant to this report

Objectives	Outcome variables
To investigate the pharmacodynamic (PD)-PK relationship for cediranib and blood pressure (BP).	Cediranib plasma concentration following dosing on Day 14. Day 14 PK parameters (AUC_{ss}, $C_{ss,max}$, $C_{ss,min}$). Maximum change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) observed for each patient between study Days 7 and 28 (whilst on study treatment). 24 hr ambulatory blood pressure for each patient on Day 14.
To determine the safety and tolerability of cediranib in combination with antihypertensive medication.	Adverse events, laboratory findings (clinical chemistry, haematology, urinalysis), vital signs, physical examination, electrocardiogram (ECG).
Exploratory	
To investigate the relationship between the effects of cediranib on angiogenesis biomarkers and clinical efficacy.[b]	Absolute levels and percentage changes from baseline in biomarkers of disease activity and angiogenesis including vascular endothelial growth factor (VEGF), soluble vascular endothelial growth factor receptor 2 (sVEGFR-2), fibroblast growth factor (bFGF) and circulating endothelial cells (CECs).[c]

[a] Duration of response was not a protocolled efficacy variable. It was added to the analysis of efficacy in order to make this study consistent with other studies in the cediranib clinical programme.

[b] In this report, there was no further analysis of the relationship between biomarkers and efficacy as this was fully described in the primary analysis.

[c] The Clinical Study Protocol (CSP) stated that placental growth factor (P1GF), hepatocyte growth factor (HGF) would be evaluated during this study. In practice data for these biomarkers were not collected, but fibroblast growth factor (bFGF) was evaluated although it was not listed in the variables in the CSP. The samples obtained for CEC analysis were non-analysable and therefore it has not been possible to present any results as planned in the protocol.

Study design

This was a Phase II, randomised, double-blind, factorial, multi-centre study designed to identify a treatment strategy, consisting of a dose of AZD2171 (RECENTIN™, cediranib; 30 mg or 45 mg) and a hypertension management strategy (pre-defined management of emergent hypertension +/- prophylaxis), that was well tolerated without significant drug withdrawal or dose reduction during the first 12 weeks of treatment with cediranib. Patients were randomised in a ratio of 1:1:1:1 to 1 of the 4 treatment groups: cediranib 30 mg with antihypertensive (antiHT) prophylaxis, cediranib 30 mg with no antiHT prophylaxis, cediranib 45 mg with antiHT prophylaxis, or cediranib 45 mg with no antiHT prophylaxis.

Patients randomised to antiHT prophylaxis treatment were to receive a low therapeutic dose of a calcium channel antagonist 3 days to 7 days prior to starting cediranib, unless their blood pressure (BP) was <110/70 mmHg in which case they started prophylaxis at the same time as the initial dose of cediranib. For patients already on treatment with a calcium-channel antagonist prior to the study, the prophylactic treatment strategy consisted of a dose increase of the agent being prescribed. The hypertension treatment allocation was not blinded. Randomisation to the hypertension management strategies was stratified by current use of medication for hypertension.

Target subject population and sample size

Male and female patients aged ≥18 years with a World Health Organisation (WHO) performance status between 0-2 and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) guidelines. **Key inclusion criteria:** histological or cytological confirmation of advanced solid tumour (with the exception of prostate cancer which was excluded), refractory to standard therapies or for which no standard therapy existed and for which there was a rationale for the therapeutic use of a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor; 1 or more measurable lesions at least 10 mm in the longest diameter by spiral computed tomography (CT) scan or 20 mm with conventional techniques (as defined by RECIST).

The primary analysis was done on an intention to treat (ITT) basis and included all randomised patients on the basis of their randomised treatment. The planned sample size for the study was 120 patients, with 30 patients per randomised group.

Investigational product: dosage, mode of administration and batch numbers

Cediranib was administered orally, once daily as a 1 x 30 mg tablet plus 1 x 15 mg placebo tablet (ie, total cediranib dose of 30 mg) or 1 x 30 mg tablet plus 1 x 15 mg tablet (ie, total cediranib dose of 45 mg). Batch numbers are provided in the CSR.

Duration of treatment

Patients could continue daily dosing indefinitely, assuming that they did not meet a withdrawal criterion, were free from intolerable toxicity and, in the investigator's opinion, were receiving some benefit from therapy.

Statistical methods

No formal statistical analyses were performed on the data presented in this report.

Subject population

One hundred and thirty-three patients were enrolled into this study, 126 patients were randomised and of these 119 received treatment. Forty-eight patients were ongoing at the primary data cut-off. One patient was ongoing at the time of the current data cut-off.

Overall the demographic and baseline characteristics were balanced across the treatment groups and representative of the target population (patients with advanced solid tumours).

Summary of efficacy results

Two additional partial responses (PRs) were recorded in the final analysis, making a total of 11 patients with PRs; 3 breast cancer, 2 melanoma, 2 renal, 1 sarcoma, 1 prostate, 1 cervix, 1 head and neck (renal and head and neck cancer were new in the final analysis compared with the primary analysis). As observed in the primary analysis, the objective response rate and stable disease rate were similar across all 4 treatment groups. The final analysis showed a median duration of response for the 11 responders of approximately 1 year. The longest

response to treatment was 913 days in a patient with cancer of the cervix in the 30 mg no prophylaxis group (the patient had not progressed at the time of data cut-off).

There was no clear difference between the 4 treatment groups in terms of median best change from baseline in tumour size (range 0 to -19.5).

Summary of pharmacokinetic results

An additional footnote (footnote a) has been added to the following table for clarification.

Table S2 Cediranib steady-state PK parameters grouped by dose and treatment group on Day 14: PK analysis set

PK parameters	Summary statistics	Cediranib 30 mg		Cediranib 45 mg	
		AntiHT prophylaxis	No AntiHT prophylaxis[a]	AntiHT prophylaxis	No AntiHT prophylaxis[a]
AUC_{ss} (ng/mL.h)	Gmean (CV%)	1200 (56.6)	854 (72.6)	1770 (68.3)	1040 (139.2)
$C_{ss,max}$ (ng/mL)	Gmean (CV%)	85.8 (49.0)	79.3 (80.2)	128 (58.2)	84.0 (157.0)
$C_{ss,min}$ (ng/mL)	Gmean (CV%)	28.3 (85.8)	19.1 (82.8)	51.0 (85.1)	21.9 (153.3)
t_{max} (h)	Median (range)	3.0 (0.0 to 6.0)	3.0 (0.8 to 6.4)	3.0 (1.9 to 6.0)	3.0 (0.0 to 6.1)

The number of patients contributing data for each PK parameter estimate is as follows:
AUC_{ss}: n=9, n=13, n=6 and n=13, respectively for each group in the table above (left to right).
$C_{ss,max}$: n=9, n=15, n=7 and n=13
$C_{ss,min}$: n=9, n=15, n=6 and n=13
t_{max}: n=9, n=15, n=7 and n=13

[a] The category of no antiHT prophylaxis refers to the group the patient was randomised to, ie, whether or not they were randomised to receive prophylactic antiHT medication prior to starting treatment with cediranib, which is not necessarily the same as the patients antiHT status by the time the PK samples were collected on Day 14; all patients could receive hypertension treatment if hypertension emerged. By Day 14, the majority of patients in both the 30 mg and 45 mg no antiHT prophylaxis groups had received antiHT treatment.

Summary of pharmacodynamic results

The plasma levels for fibroblast growth factor (bFGF), vascular endothelial growth factor-A (VEGF) and soluble vascular endothelial growth factor receptor 2 (sVEGFR-2) obtained in between 26 January 2007 and 2 September 2009 in patients who were ongoing in the study, and who provided further samples, did not alter the conclusions of the primary analysis.

Summary of pharmacokinetic/pharmacodynamic relationships

Evaluation of the PK/PD relationship in patients who had evaluable PK data following dosing on Day 14 and appropriate BP data between Days 7 and 28 indicated that there was no clear relationship between AUC_{ss}, $C_{ss,min}$ and $C_{ss,max}$ and the maximum change from baseline in BP between Days 7 to 28. This observation is not unexpected, given that the majority of patients randomised at baseline to either the 30 or 45mg no antiHT prophylaxis groups had received antiHT treatment by the time the first post-dose BP measurement was collected (Day 7).

Therefore the majority of patients included in the PK/PD evaluation had received antiHT treatment. A clear relationship would not be expected when assessing patients who had already received treatment for hypertension.

Summary of safety results

At the primary analysis, the mean actual exposure to study treatment across the 4 treatment groups was in the range 95.9 to 114.9 days. In the final analysis, the mean actual exposure to study treatment across the 4 treatment groups was in the range 133.5 days to 199.6 days.

In the final analysis, the proportion of patients with a dose reduction and/or pause only increased slightly with increased follow-up. The proportions of patients who had a dose reduction or a dose pause were similar in all treatment groups. The majority of patients with a dose reduction only had 1 dose reduction (42/57). The total duration of dose pauses for a patient was 14 days or less for the majority of patients (46/67).

Compared with the primary analysis, the increase in the number of patients reporting each type of adverse event (AE) was small in relation to the increased duration of follow up/exposure.

Table S3 Number of patients who had at least 1 AE in any category: Safety analysis set

AE category	Number (%) of patients[a]			
	Cediranib 30 mg		Cediranib 45 mg	
	AntiHT prophylaxis N=28	No-AntiHT prophylaxis N=31	AntiHT prophylaxis N=26	No-AntiHT prophylaxis N=34
Any AE	**28 (100.0)**	**31 (100.0)**	**26 (100.0)**	**34 (100.0)**
Any AE of CTCAE[b] grade 3 or higher	23 (82.1)	22 (71.0)	21 (80.8)	28 (82.4)
Any AE with outcome = death	0	1 (3.2)	2 (7.7)	0
Any SAE (including events outcome = death)	11 (39.3)	20 (64.5)	14 (53.8)	24 (70.6)
Any AE leading to discontinuation of cediranib	4 (14.3)	4 (12.9)	8 (30.8)	9 (26.5)
Any other significant AE (OAE)	0	0	0	0

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] CTCAE Version 3.0.

The nature of the AEs reported in the final analysis was similar to that observed in the primary analysis. Given the increase in duration of follow up and exposure to study drug, an increase in incidence of AEs was expected. No increases in incidence of any individual AE represented a change in the known safety profile of cediranib. There were no new hypertension-related AEs or serious adverse events (SAEs).

No new deaths due to an AE were reported in the final analysis compared with the primary analysis. There were 19 more deaths as a result of disease progression.

In total, 10 more patients had an SAE in the final analysis compared with the primary analysis. In addition, there were 5 patients who had an SAE in the primary analysis who had an additional SAE in the final analysis.

Eight more patients discontinued investigational product due to an AE in the final analysis. No patients had any other significant AE.

Haematology, clinical chemistry and urinalysis data from the final analysis were consistent with the primary analysis.

As observed in the primary analysis, the average absolute changes in mean systolic and diastolic BP were similar in all treatment groups. The minimum and maximum values of BP variables were also similar in all treatment groups.