AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00015
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An Exploratory, Open-Label Study to Assess the Effects of AZD2171 on Tumours and Biomarkers in Patients with Previously Untreated or Recurrent Non-Small Cell Lung Cancer (NSCLC) or Patients with Metastatic or Recurrent Head and Neck Cancer (HNC)

Study dates: First patient enrolled: 22 December 2005
Last patient completed: 1 July 2009

Phase of development: Clinical pharmacology (I)

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

Study centres: 1 centre in Spain and 1 centre in the United States of America (US).

Publications: None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives[a]	Outcome variables
Primary	**Primary**
To explore the short-term effects of cediranib on tumours in patients with previously untreated or recurrent NSCLC and in patients with metastatic or recurrent HNC by combined assessment of: 1. Detectable changes in tumour metabolic activity determined by FDG-PET tumour SUV_{max} after 3 weeks of dosing	1. Change from baseline in tumour SUV_{max} as assessed by FDG-PET after 22, 43 and 71 days of dosing. 2. Biomarkers measured in serial tumour biopsy samples (tumour vessel density, pVEGFR-2, VEGFR-2, VEGFR-3, CD31, Ki67, apoptosis) within 7 days prior to starting treatment and prior to dosing on Day 22 +/- 2 days.
2. Biomarkers measured in serial tumour biopsy samples (VEGF signalling pathway, other angiogenesis pathways; and other related pathways, including downstream markers of activation)	3. Change from baseline in mean arterial pressure (derived from systolic and diastolic blood pressure) after 22, 43 and 71 days of dosing.
3. Mean arterial pressure	
Secondary	**Secondary**
To evaluate the safety and tolerability of cediranib by assessment of adverse events, laboratory findings and vital signs	Adverse events, laboratory findings (clinical chemistry, haematology, urinalysis), BP and vital signs, physical examination, ECGs.
Exploratory[a]	
Assess the mode of action of cediranib on tumours by assessment of tumour vessels before and after 3 weeks of treatment.	Assessment of tumour vessel density in tumour biopsies (samples as for primary biomarker variable).
Investigate the effects of cediranib on surrogate biomarkers in skin and blood.	Biomarkers in: serial skin biopsy samples (VEGF, VEGFR-2, apoptosis, Ki67, VEGFR-3) and blood (soluble markers of angiogenesis: VEGF, sVEGFR-2, bFGF, sE-selectin, PLGF, and sTie2)[b].
Explore relationships amongst changes in maximum tumour standardised uptake value and surrogate biomarkers in tumours, skin and blood.	Tumour SUV_{max}, biomarkers measured in serial skin biopsy samples, and soluble markers of angiogenesis.
Define the features of tumours and patients responding to or progressing on cediranib.	Best objective response according to RECIST
Pharmacokinetic	
Examine the relationship between tumour concentrations of cediranib to plasma concentrations of cediranib.	$C_{max,ss}$, $C_{min,ss}$, and t_{max} of cediranib in plasma and tumour samples. Insufficient tumour tissue was available for characterisation of PK in tumour samples.

bFGF: basic fibroblast growth factor; BP: blood pressure; CD31: platelet endothelial cell adhesion molecule-1; $C_{max,ss}$; maximum (peak) steady state drug concentration in plasma during dose interval; $C_{min,ss}$: minimum (trough) steady state drug concentration in plasma during dose interval; ECG: electrocardiogram; FDG-PET: 2-[F-18]-fluoro-2-deoxy-D-glucose positron emission tomography; HNC: head and neck cancer; NSCLC: non-small cell lung cancer; PK: pharmacokinetic; PLGF: placental growth factor; pVEGFR-2: phosphorylated VEGFR-2; RECIST: response evaluation criteria in solid tumours; SUV_{max}: maximum standardised uptake value; sVEGFR-2: soluble VEGF-2; t_{max}: time to reach peak maximum concentration; VEGF: vascular endothelial growth factor-A; VEGFR-2: VEGF receptor-2; VEGFR-3: VEGF receptor-3.

[a] The exploratory objectives also included collection of optional samples for retrospective pharmacogenetic analysis, which will be reported separately.

[b] This objectives also included assessment of circulating endothelial cells and VEGFR-1 (Flt-1) expressing monocytes; this will be reported separately.

Study design

Exploratory, open label, multi-centre study to investigate the short-term effects of cediranib on tumours in patients with previously untreated or recurrent non-small cell lung cancer (NSCLC) and in patients with metastatic or recurrent head and neck cancer (HNC).[1]

Target subject population and sample size

Key inclusion criteria: Patients aged ≥18 years; Histologically- or cytologically-confirmed head and neck or non-small cell bronchogenic carcinoma: adenocarcinoma (excluding bronchoalveolar), squamous (with exclusion of large central tumours) large cell carcinoma or mixed (adenocarcinoma and squamous) or undifferentiated carcinoma. Patients with NSCLC must have had unresectable Stage IIIb or Stage IV disease.

The number of patients was selected to obtain adequate safety, tolerability, tumour, biomarker, pharmacokinetic and pharmacodynamic data whilst exposing as few patients as possible to the study medication and procedures.

Investigational product: dosage, mode of administration

Cediranib 30 mg was administered once-daily oral tablet for 3 weeks or until disease progression, unacceptable toxicity or self-discontinuation if sooner than 3 weeks.

Statistical methods

The primary analysis was conducted for the 2 [F-18]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), and Response Evaluation Criteria in Solid Tumours (RECIST) data approximately 10 weeks after the last subject entered the study. The final analysis was conducted when all patients had discontinued from the study. Statistical analyses were performed in the group of patients who received cediranib 30 mg monotherapy.

The percentage change in tumour maximum standardised uptake value (SUV_{max}) was analysed using a t-test. The median percentage change was presented, and geometric mean percentage change and the associated 95% CI were calculated. Mean arterial pressure (MAP) was to be analysed using an analysis of variance (ANOVA) model, fitting patient and planned day as factors. The change from baseline with associated 95% CI was estimated. Soluble biomarkers were to be analysed in the same way as the MAP data. The changes from baseline in the soluble biomarkers were analysed using an ANOVA model, when the data met the assumptions of ANOVA model. Otherwise a non-parametric method was applied. Best objective response / overall response rate assessed by RECIST was tabulated by patient population (HNC or NSCLC). The percentage change in tumour size from baseline was calculated and summarised by patient population. Other data were summarised descriptively.

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[1] The study was originally designed as a comparator study but was amended to a monotherapy study (removing gefitinib alone and gefitinib combination arms) (Amendment 02, 1 November 2006). The primary reason for this amendment is that in the US, gefitinib was no longer indicated for patients with NSCLC in the US.

Subject population

Thirty-six patients were enrolled in the study. This included patients recruited to gefitinib treatment arms in the original protocol design, prior to their removal in Amendment 02. Twenty-four patients received treatment; 7 patients under the original study design (cediranib/gefitinib combination) and a further 17 patients under the revised design (cediranib alone). Two patients in the original study design received cediranib 30 mg + gefitinib placebo, and were therefore included in the cediranib 30 mg analyses. Patients were representative of the target population.

Summary of efficacy results

Change from baseline in tumour SUV_{max} at Day 22 was a primary objective. SUV_{max} was reduced by a median of 10.58% at Day 22 of treatment with cediranib 30 mg alone. This reduction was maintained at subsequent visits (on Day 43 and 71 of treatment). In the exploratory objective of response according to RECIST, reductions in tumour size were seen on Day 43 and 71 of study treatment. Overall, the mean best percentage change was a 25.9% reduction in tumour size. Overall, 74% (14/19) of patients reported a best response of either partial response or stable disease: 21% and 53%, respectively.

Summary of pharmacodynamic results

Assessment of biomarkers measured in serial tumour biopsy samples was a primary objective. However, in this study, the tissue marker data were too variable and the sample set too small to draw conclusions about the effects of cediranib on the tumour biomarkers investigated.

MAP is potentially a strong biomarker for the activity of cediranib since vascular endothelial growth factor (VEGF) is an endogeneous vasodilator and was originally to be assessed as a primary objective. However, as the study progressed, the choice of MAP as a marker was considered compromised since there were guidelines in place during the study to manage high blood pressure. Thus, the data collected are presented in the CSR, but cannot be interpreted as a biomarker.

Additional exploratory biomarker objectives were also investigated. Assessment of soluble biomarkers showed increases in VEGF and placental growth factor (PLGF), and decreases in soluble vascular endothelial growth factor receptor-2 (sVEGFR-2). Correlations between soluble biomarker levels and FDG-PET SUV_{max}, or change in tumour size, were not observed. Interpretation of tumour vessel density and skin biopsy data could not be performed as the tissue biomarker data were too variable.

Summary of pharmacokinetic results (exploratory objective)

There was insufficient tumour tissue obtained to allow the tumour concentrations of cediranib to be determined, therefore the relationship between tumour and plasma cediranib concentrations could not be explored.

Summary of safety results

The average daily dose of cediranib was 28.0 mg. Two patients experienced a dose reduction, and 11/19 patients experienced at least one dose pause. Dose pauses occurred on single instances (typically of ≤14 days duration).

The observed safety profile of cediranib 30 mg in this study appeared to be consistent with the current emerging safety profile of cediranib. There were no new or unexpected safety findings. All patients included in the safety population experienced at least 1 adverse event (AE) during the course of the study. The most commonly reported AEs were proteinuria (42%), diarrhoea (42%), fatigue (32%) and hypertension (32%). No patients died because of an AE. Three patients had serious adverse events (SAEs) (acquired tracheo-oesophageal fistula, anaemia, hypovolaemia, nausea, tongue haemorrhage and vomiting, all in the HNC group). Two patients, both in the HNC group, had AEs leading to discontinuation of treatment (tongue haemorrhage [SAE] and asthenia).

Ten (52.6%) patients experienced AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher (fatigue [4 patients], diarrhoea [3 patients], asthenia [2 patients], hypertension [2 patients], and acquired tracheo-oesophageal fistula, dyspnoea, hypokalaemia, tongue haemorrhage and weight decreased in 1 patient each). The AE of tongue haemorrhage was the only Grade 4 event. Increases in thyroid-stimulating hormone occurred during treatment, and recovery was observed. Development of proteinuria was observed. Haematology and other clinical chemistry data were unremarkable. Blood pressure elevations to moderate or severe hypertension were observed in few patients. There were no clinically important changes in electrocardiogram data.