AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00054
Edition Number	1
Date	15 July 2010

A Phase I, Multi-Center, Open-Label, Dose Selection Study to Assess the Safety and Tolerability of Cediranib (RECENTIN™, AZD2171) in Combination with Etoposide and Cisplatin (EP) as First Line Therapy for Lung Cancer Patients with Extensive Stage or Metastatic Disease for Whom EP Would be a Standard Therapy

Study dates: First patient enrolled: 4 February 2008
Last patient enrolled: 15 June 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

This was a multi-centre study; it was conducted at 4 centres in the USA.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary: To assess the safety and tolerability of cediranib in combination with etoposide and cisplatin (EP).	**Primary:** Adverse events, vital signs, clinical chemistry, haematology, urinalysis (including creatinine clearance), ECG, physical examination, thyroid function test.
Secondary:	**Secondary:**
To make a preliminary assessment of the efficacy of cediranib in combination with etoposide and cisplatin.	Best tumour response (CR, PR [only possible for patients with measurable disease], SD, PD, NE), RR (frequency of CRs and PRs), change from baseline in tumour size (only for patients with measurable lesions), progression-free survival, duration of response for responders (based on RECIST).
To compare the PK parameters of etoposide given in combination with cisplatin only, to etoposide given in combination with both cisplatin and cediranib.	Single dose PK parameters of etoposide given in combination with cisplatin only versus in combination with both cisplatin and cediranib: C_{max}, $AUC_{(0-t)}$, AUC, CL, $t_{1/2\lambda z}$, MRT and t_{max} on Days 1 and 22.
To determine the steady-state PK parameters of cediranib when given in combination with etoposide and cisplatin.	Multiple dose PK parameters of cediranib when given in combination with etoposide and cisplatin: $C_{ss,max}$, $C_{ss,min}$, t_{max}, AUC_{ss} on Day 22.
Exploratory:	
To investigate the effects of cediranib on blood (serum and plasma)-based biomarkers.	Biomarker levels and percentage changes from baseline in plasma biomarker levels: VEGF, sVEGFR-2, CECs[a].
To investigate the relationship between biomarkers in serum and plasma and the clinical efficacy of cediranib.	VEGF, sVEGFR-2 and CECs[a] levels and changes from baseline vs. efficacy variables: tumour size, best tumour response group at Screening, Days 1, 3, 22, 24, and at treatment discontinuation.

CEC Circulating endothelial cells; CR Complete response; CSP Clinical Study Protocol; NE non evaluable; PD Progressive disease; PFS Progression free survival; PK Pharmacokinetic; PR Partial response; RECIST Response Evaluation Criteria in Solid Tumours; RR response rate; SD Stable disease.

[a] CEC analysis was considered a potential pharmacodynamic biomarker when the CSP was written, but based on experience, analysis of CEC data was not confirmed to be a meaningful pharmacodynamic (or predictive) biomarker for cediranib and so no analysis was performed.

Study design

Phase I, open-label, multiple-centre, dose-selection study to assess the safety and tolerability of cediranib in combination with etoposide and cisplatin (EP) as first line therapy for lung cancer patients with extensive stage or metastatic disease for whom EP would be a standard therapy. The starting dose of cediranib for the first cohort of patients was 30 mg (4 patients

only). However, this dose level was amended to 20 mg following the introduction of a protocol amendment that took into account all available data.

Target subject population and sample size

Patients aged 18 years or older with the following cancer diagnosis and stage: histological or cytological confirmed extensive stage Small Cell Lung Cancer or other neuroendocrine carcinomas of the lung.

The number of patients was based on the desire to obtain adequate safety and tolerability data whilst exposing as few patients as possible to the study medication and procedures.

Investigational product and comparator(s): dosage, mode of administration

Etoposide was administered as iv infusion, 100 mg/m^2; cisplatin was administered as iv infusion, 80 mg/m^2; cediranib was supplied as 15 mg, 20 mg and 30 mg tablets. Cediranib was to be administered orally, once daily in the morning and no less than 1 h prior to the consumption of a meal or at least 2 h after a meal. After discontinuation of study drug for any reason, the subsequent choice of treatment was at the discretion of patient and investigator. If toxicity attributable to cediranib was encountered the dose was to be reduced.

Duration of treatment

Patients received etoposide (on Days 1, 2, and 3) and cisplatin (on Day 1) every 3 weeks (21-day cycle length), for 4 to 6, cycles. Patients also received single daily doses of cediranib starting on Day 4 of Cycle 1 and continuing for the duration of participation.

After completing EP chemotherapy, patients could continue with cediranib as monotherapy until progression was confirmed; for those patients continuing to gain symptomatic benefit after objective disease progression, treatment could be continued. If treatment with EP was stopped for any reason, patients could continue once-daily oral dosing with cediranib alone indefinitely.

Statistical methods

The primary objective of the study was concerned with safety and tolerability. There were no formal analyses of safety data in this study; all safety data were listed, summarised and plotted descriptively only. The only data that were to be formally analysed were etoposide C_{max}, $AUC_{(0-t)}$ and AUC parameters. However, owing to the limited data obtained in the study, this analysis was not performed. All other data were listed, summarised and plotted descriptively.

Subject population

In total, 26 patients were enrolled, of which 22 patients received study treatment: 4 patients were treated with cediranib 30 mg (cohort 1) and, following the introduction of a protocol amendment, 18 patients were treated with cediranib 20 mg (6 in cohort 2 and 12 in the expansion cohort). A total of 9 patients were still ongoing in the study at the time of data cut-off (7 August 2009).

Summary of safety results

During the dose selection process with cediranib 20 mg plus etoposide and cisplatin, 1 out of 6 (<33%) patients reported a DLT of haemoptysis attributed to cediranib thereby fulfilling the pre-defined protocol MTD criteria and the combination was declared tolerable. The cohort was expanded to 12 more patients, who also tolerated this combination to provide greater reassurance on the tolerability of this regimen.

Exposure: Average duration of exposure to cediranib 30 mg and 20 mg during the whole study was 183 and 132 days, respectively. Mean daily doses in the first 12 weeks were approximately 28 and 19 mg, respectively. There were no dose reductions in the cediranib 20 mg group and 2 dose reductions in 1 patient in the cediranib 30 mg group. Half the patients in each treatment group had no dose pauses. Although there appeared to be some delays in the chemotherapy, these did not appear to be cumulative such that, in general, the patients did not appear to have fewer cycles over a fixed time period than they would otherwise have had.

AEs: Most common AEs reported in the cediranib 30 mg group were nausea, hypomagnesaemia, fatigue and thrombocytopenia, each reported by 3 (75%) of patients. The most common AEs reported in the cediranib 20 mg group were nausea, neutropenia, diarrhoea and hypomagnesaemia reported by 12 (66.7%), 12 (66.7%), 11 (61.1%) and 10 (55.6%) of patients, respectively. The AE profile for cediranib 30 mg and cediranib 20 mg seen in this study was broadly consistent with the AE profile seen in previous cediranib studies. Hypomagnesaemia and electrolyte imbalance are AEs commonly associated with cisplatin.

One patient died during the study, before the time of data cut-off for this CSR. The patient had an SAE of sepsis with an outcome of death (and concomitant haemoptysis), and death was considered by the investigator to be related to the disease under investigation. The patient died 3 days after having received just one dose of cediranib 30 mg.

SAEs were reported for 1 (25%) patient in the cediranib 30 mg group and 10 (55.6%) patients in the cediranib 20 mg group. AEs that led to discontinuation were reported for 1 (25%) patient in the cediranib 30 mg group and 4 (22.2%) patients in the cediranib 20 mg group.

Expected AEs were generally well managed by supportive care, dose reductions and dose pauses. The AE profile for cediranib 30 mg and cediranib 20 mg seen in this study was broadly consistent with the AE profile seen in previous cediranib studies.

Clinical laboratory data: There were no new findings related to clinical laboratory evaluations compared with previous cediranib studies.

Vital signs and ECGs: The incidence of hypertension reported as an AE was lower (45.5%) than previously reported in cediranib studies at this dose. The ECG data did not give any cause for concern for safety with regard to cediranib treatment.

Summary of efficacy results

The majority of patients showed tumour responses that were either partial responses or stable disease: 3 out of 4 patients (75%) overall in the cediranib 30 mg group, 14 out of 18 patients (77.8%) overall in the cediranib 20 mg group. No complete responses were reported in either group.

The PFS data were not considered reliable given the high level of censoring and the small number of patients.

The best mean percentage change from baseline in target tumour size was -72.1% and -53.3% in the cediranib 30 mg (N=3) and 20 mg (N=17) groups, respectively. A sustainable change from baseline in tumour size was apparent in both treatment arms.

The mean duration of tumour response was 368.5 days ranging from 260 to 477 days (12.1 months, ranging from 8.5 to 15.7 months) days in the cediranib 30 mg group and 125.8 days ranging from 47 to 263 days (4.1 months, ranging from 1.5 to 8.6 months) in the cediranib 20 mg group. At data cut-off, in the cediranib 30 mg group there was 1 patient ongoing and still in response with response duration of 477 days (15.7 months); in the 20 mg group there were 5 patients ongoing and still in response with response duration ranging from 50 to 156 days (1.6 to 5.1 months) (3 other patients were ongoing without being in response).

In general the tumour responses appeared durable: in the cediranib 30 mg group, 2/4 patients had a response of at least 8.5 months (260 days); in the cediranib 20 mg group, 10/18 patients showed a response of at least 3 months (91 days) and 3/18 patients showed a response of at least 5 months (152 days).

Summary of pharmacokinetic results

There were insufficient data to draw meaningful conclusions about the PK parameters of etoposide. The 20 mg steady state PK parameters of cediranib were similar to those seen in previous cediranib studies at the same dose.

Summary of pharmacodynamic results

sVEGFR-2 and VEGF levels showed decreases and increases from baseline, respectively, at Day 22 of treatment, with no correlation between baseline levels, or changes on Day 22, and changes in tumour size or response.