AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib
Study Code	D8480C00060
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A Phase I, randomised, multi-centre, open-label study to determine the pharmacokinetics and tolerability of cediranib (RECENTIN™, AZD2171) following a single and multiple oral 20mg or 30 mg doses in Chinese patients with advanced solid malignancies

Study dates: First subject enrolled: 18th Sep 2009
Last subject last visit: 24th Mar 2010

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

This phase I, multi-centre study was conducted in 20 patients with advanced solid malignancies. One centre in China mainland and 1 in Hong Kong participated in the study.

Publications

None.

Objectives and criteria for evaluation

The primary objective of this study was to assess the pharmacokinetics of single dose of cediranib 20 mg or 30 mg in Chinese patients with advanced solid malignant tumours.

- Single dose PK parameters:

Cmax, tmax, AUC, AUC (0-t), AUC (0-24h), t1/2λz, MRT, Vss/F and CL/FSecondary objective

The secondary objectives of the study were:

- To assess the pharmacokinetics of multiple doses of cediranib 20mg or 30 mg in Chinese patients with advanced solid malignant tumours. Multiple dose PK parameters:
  - Css,max, Css,min, tmax, AUCss, Rac and TCP0
- To assess the safety and tolerability of single and multiple doses of cediranib 20 mg or 30 mg in Chinese patients with advanced solid malignancies.

The exploratory objective of this study was:

- To assess the anti-tumour activity of cediranib 20mg or 30 mg daily oral dose in Chinese patients with advanced solid malignancies.

Study design

This multi-centre, randomized, parallel group, open-label study consisted of a single dose phase and a multiple doses phase to assess the pharmacokinetics parameters of cediranib 20 mg or 30 mg once daily dose in Chinese patients with malignant solid tumours.

Target subject population and sample size

Patients were aged 18 years or over and had histologically or cytologically confirmed advanced solid malignancies that was refractory to conventional therapeutic modalities or no appropriate therapies exist.

At least 8 patients perdose level out of the16 total with advanced solid malignancies received a single dose of cediranib 20 mg or 30 mg (Day 1) orally and after 6-days washout period, the

patients began oral administration of cediranib once daily at the same dose as received in Day 1.

To be evaluable for single dose PK, patients had to receive a single dose. For multiple dosing, patients must had to take cediranib for seven days continuously without interruptions or reductions prior to PK sampling on days 8, 15, 22 & 29.

For single dose parameter of AUC, if the variation in CV (%) observed in the Chinese population was consistent with the Western population (70%), it was expected that the mean exposure observed would be within 53% of the true mean. Similarly for single dose parameter of Cmax, if the variation in CV (%) observed in the Chinese population (60%) was consistent with the Western population, it was expected that the mean exposure observed would be within 44% of the true mean.

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

AZD2171 was manufactured and supplied by AstraZeneca as brown, film-coated tablets in 15, 20, and 30 mg dosage strengths. The batch (ADM) numbers were as follows: 15 mg 7374.2/1, 20 mg 7374.2/2, and 30 mg 7374.2/3.

The tablet(s) were administered orally with appropriate volume of water (approximately 240 mL) with the patient in an upright position. On days when blood samples were collected for pharmacokinetics evaluation, patients were instructed to not take their study drug until a pre-dose pharmacokinetics sample was collected.

Duration of treatment

Single dose phase: Patients received a single dose of cediranib 20 mg or 30 mg followed by a 6-days washout period.

Multiple dose phase: Patients began daily oral administration with cediranib 20mg or 30 mg and continued at this dose with the exception of dose reduction as detailed below. After completion of the multiple dose PK assessments, patients were allowed to continue with daily dosing of Cediranib indefinitely, assuming that they did not withdraw informed consent, meet a withdrawal criterion, were free from intolerable toxicity and, in the investigator's opinion, were receiving some benefit from the therapy.

Statistical methods

A comprehensive Statistical Analysis Plan (SAP) was prepared and finalised before database lock. All statistical analyses were carried out under the direction of the Biostatistics Group, AstraZeneca.

The main analysis took place when the full PK data were available, subsequent safety assessments were to continue to be performed until the patient was withdrawn from the medication with Cediranib.

No formal statistical analysis was performed on the safety and efficacy data from the study. Listings and summaries were generated and descriptive statistics by dose were used.

Subject population

In total, 20 patients were enrolled into this phase I, multi-centre study and received study treatment. The data cut-off for this CSR was 4 May 2010, at which time 9 (45.0%) patients were ongoing, with 5 (55.6%) in the cediranib 20mg arm and 4 (36.4%) in the cediranib 30mg arm. According to the protocol amendment, following the data cut off protocolled data collection was to be reduced to SAEs only. The SAE data collected after data cut off will be summarised in an additional report..

Generally the two arms were well balanced by the age, Sex and baseline BMI. The mean age was 56 years. All the patients were Asian (100.0%). The majority of patients were female (60.0%) and aged between 18 and 65 years (80.0%). The baseline BMI was 23.1(kg/m2).

The type of cancer was generally well balanced between cediranib 20mg arm and cediranib 30mg arm. The majority of tumor types were lung (77.8% for cediranib 20mg arm versus 72.7% for cediranib 30mg arm, respectively).

More patients presented with WHO PS1 (70% versus 30% for PS0). A slight imbalance was noted in the proportion of patients with PS0 (44.4% versus 18.2% for the cediranib 20mg and cediranib 30mg arms, respectively). The majority of histology type was adenocarcinoma (NOS) [11pts (55.0%)] and adenocarcinoma [6 pts (30.0%)].

Summary of efficacy results

According to the limited data, there showed some anti-tumour activity of cediranib in Chinese patients with advanced solid malignancies:6 (30.0%) stable disease (SD), with 3 (33.3%) in cediranib 20mg arm and 3 (27.3%) in 30mg arm.

Summary of pharmacokinetic results

Following both single and multiple doses there was relatively large inter-patient variability observed, with an overlap in exposures between the 20mg and 30mg doses; the highest exposure was observed in the 20mg dose group. In both dose groups the PK was as expected over time following multiple dosing. There was some limited accumulation following multiple dosing, as would be expected based on the mean $t1/2\lambda z$ of approximately 20 hours (maximum 39.6h).

The single and multiple dose PK parameters obtained here was similar to the results obtained at the same doses in Western (D8480C00001,D8480C00020) and Japanese (D8480C00023) patients. In all studies relatively large inter-patient variability was observed.

Summary of pharmacodynamic results (Not applicable)

Summary of pharmacokinetic/pharmacodynamic relationships (Not applicable)

Summary of pharmacogenetic results (Not applicable)

Summary of safety results

The safety data presented in this section represents the primary analysis with a data cut off on the 4th May 2010 for all 20 patients in the study. In total, all patients in the study received at least one dose of cediranib.

All 20 patients included in this study experienced one or more AEs. A total of 18 (90.0%) patients experienced an adverse event that was considered by the investigator to be related to treatment.

The most frequently reported adverse events were diarrhea (11 [55.0%]), hypertension (10 [50.0%]) and proteinuria (4 [20.0%]).There appeared some evidence of a dose relationship for hypertension.

The most commonly reported drug-related adverse events were hypertension (10 [50.0%]), diarrhoea (10[50.0%]) and proteinuria (4[20.0%]). There appeared some evidence of a dose relationship for hypertension.

There were no drug-related CTC Grade 3 or 4 AEs at cediranib 20 mg arm. Four drug-related CTC Grade 3 or 4 AEs at cediranib doses of 30 mg arm were hypertension (2 [10.0%]), oedema peripheral (1 [5.0%]), pleural effusion (1[5.0%]). All the events were of CTC grade 3.

Two patients were reported to have died as a result of an adverse event. The AEs associated with the deaths were coma (E0001997, cediranib 30mg), pulmonary embolism (E0002999, cediranib 30mg). None of these deaths was considered by the investigator to be caused by cediranib.

Three patients (15.0%) had 5 SAEs other than deaths during the study. Ascites, oedema peripheral, hypoalbuminaemia and pleural effusion accounted for 2, 1, 1 and 1 of the events respectively.

One patient (E0001990) experienced a total of 2 SAEs other than death that were considered by the investigator to be related to study treatment. The 2 SAEs were hypoalbuminemia and pleural effusion.

A total of 3 (15.0%) patients discontinued due to 4 AEs in the study, which were hypoalbuminemia, coma, pulmonary embolism and ascites, all in cediranib 30mg arm. Only hypoalbuminemia was considered drug-rlated.

With the exception of BP, there were no clinically relevant trends in vital signs, laboratory parameters,physical finding, or ECG observations.