AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2281 (olaparib, KU-0059436)
Study Code	D0810C00001
Edition Number	1
Date	7 October 2009

A Phase I, open-label, dose escalation study to assess the safety and tolerability of AZD2281 following single and multiple oral doses in patients in Japan with advanced solid malignancies

Study dates: First patient enrolled: 22 November 2007
Last patient completed: 18 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 centre(s)

This study was a single centre study. A minimum of 3 patients with advanced solid malignancies were recruited at each dose level. A maximum of 18 patients were planned to be enrolled (maximum of 6 patients were to be enrolled into each dose level).

Publications

None at the time of writing this report.

Objectives

Primary objectives

The primary objective of this study was to determine the safety and tolerability of AZD2281 with respect to the following outcome variables:

- Adverse events (AE), clinical laboratory tests, vital signs (blood pressure, pulse rate, body temperature), Electrocardiogram (ECG), chest X-ray, respiratory tests.

Secondary objectives

The secondary objectives of the study were:

- To determine the pharmacokinetic (PK) profile of oral AZD2281 with respect to the following outcome variables.
  - PK parameters: Maximum plasma (peak) drug concentration (C_{max}), Time to maximum concentration (t_{max}), Area under the plasma concentration-time curve from time 0 to t ($AUC_{(0-t)}$), Area under plasma concentration-time curve from zero to infinity (AUC), Terminal half-life ($t_{1/2}$), Apparent Oral Clearance (CL/F), Apparent volume of distribution at steady state (V_{ss}/F), Mean residence time (MRT)
- To determine the maximum tolerated dose (MTD) according to Dose Limiting Toxicity (DLT).

Exploratory objectives

The exploratory objectives of the study were:

- To determine the PARP Inhibitory Dose (PID) range in a surrogate for tumour tissue, Peripheral Blood Mononuclear Cells (PBMC).
  - PARP inhibitory activity in PBMC

- To investigate the PK-pharmacodynamic (PD) (PARP inhibitory activity in PBMC) profile of AZD2281.
  - Exposure in blood plasma
  - PARP inhibitory activity in PBMC
- To enable a preliminary assessment of the anti-tumour activity of AZD2281.
- Tumour response (according to Response Evaluation Criteria in Solid Tumours (RECIST) guideline)

Study design

This study was a Japanese single-centre, open-label, dose escalation phase I trial. The study involved two phases: ascending dose phase and expanded cohort phase which were divided into the following two periods for evaluation of dose: (a) a single dose period, dosing on the morning of Single Dose Period Day 1 followed by (b) a multiple dose period of continuous dosing for 28 days starting on the morning of Multiple Dose Period Day 1 (48 hours after the initial single dose on Dingle Dose Phase Day 1).

Target patient population and sample size

Adult patients with histologically or cytologically confirmed solid malignancy that had progressed despite standard therapy or for whom no standard therapy exists were to be enrolled onto the study. It was expected that approximately 18 patients at maximum were enrolled.

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

For this study, AZD2281 capsule was in one dosage strength: 50 mg, size 0, coloured white. The batch number was BMR/07/512/A.

At the single dose period, AZD2281 (from 100 mg up to 400 mg) was given orally 1 hour after breakfast (once a day). During the multiple dose period, AZD2281 (from 100 mg bd up to 400 mg bd) was administered orally approximately 1 hour after morning and evening food. AZD2281 was administered at approximately the same times each day, if possible. The patient then refrained from eating for a further 2 hours post dose. The dose interval was preferably approximately 12 hours.

Duration of treatment

For the purposes of the protocol, cycles nominally lasted for 28 days. Patients continuing to tolerate the treatment without DLT repeated this schedule until such time as no clinical benefit was apparent (ie, patient has progressive disease), or the patient was withdrawn for other reasons.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

- PK
  - PK parameters: C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$, CL/F, V_{ss}/F, MRT
- PD
  - PARP inhibitory activity in PBMC
- Efficacy
  - Tumour response (according to RECIST guideline)

Criteria for evaluation - safety (main variables)

- Safety
  - AEs
  - Clinical laboratory tests
  - Vital signs (blood pressure, pulse rate, body temperature)
  - ECG
  - Chest X-ray
  - Respiratory tests

Statistical methods

Descriptive statistics and data listings were to be used to describe the trial population, safety, tolerability, PK and PD data, and the observed anti-neoplastic response. All reported symptoms and AE were coded according to the Common Terminology Criteria for Adverse Events (CTCAE)- Medical dictionary for regulatory activities (MedDRA) coding system and presented and summarized by dose. Crude incidence rates were based on the maximum intensity grade for each patient.

Study results

Patient population

Overall, 12 patients (3 patients in 100 mg bd group, 3 patients in 200 mg bd group, and 6 patients in 400 mg bd group) received study treatment. All treated patients were included in each analysis set. The study population was exclusively Asian (Japanese) in race. The mean age overall was 55.8 years.

Summary of efficacy results

Out of 12 patients with baseline RECIST data,1 patient with breast cancer experienced partial response (PR) in 100 mg bd group with a duration treatment for approximately 13 months, 4 patients (2 patients in the 200 mg bd and 400 mg bd group, respectively) experienced stable disease (SD), suggesting potential anti tumour effect of AZD2281 monotherapy in Japanese patients with solid tumours.

Summary of pharmacokinetic results

AZD2281 was administered as a single dose on Single Dose Phase Day 1, followed by continuous twice daily dosing for 28 days from Multiple Dose Period Day 1 (48 hours after the single dose). Blood samples were collected on Single Dose Phase Day 1 to Multi Dose Phase Day 1 (prior morning dose) and Multiple Dose Phase Day 15 (after the morning dose) for PK evaluation on single dose and multiple dose assumed to be at steady state, respectively. Data for PK analysis was collected in 12 cancer patients. Specifically, PK profiles were collected after administration of the single dose (Days 1) in all 12 cancer patients and collected after twice daily dose (Day 15) in 11 cancer patients. PK parameters were also calculable for 12 patients for single dose and 11 patients for multiple dose.

Following both single and twice daily administration of AZD2281, absorption of drug at all dose levels (100 mg bd, 200 mg bd and 400 mg bd) was rapid. The elimination phase was assessable only for single dose. Plasma concentrations following the peak appeared to decline biphasically and the mean terminal half-life was estimated to be between 6.86 and 10.7 hours.

Geometric mean CL/F values following single doses ranged from 7.31 to 10.8 L/h across the dose. Geometric mean V_{ss}/F values following single doses ranged between 57.6 to 107 L, indicating the distribution of the compound outside the central compartment.

By twice daily dosing, the plasma concentration and exposure of AZD2281 were increased as expected from the kinetics following single dose. However one patient (Patient E0001003) showed marked increase of plasma concentration and exposure following multiple dosing. This patient showed higher accumulation ratio of C_{max} and $AUC_{(0-10)}$ (2.78 and 5.55, respectively). Consequently, this patient showed considerably higher plasma concentration of AZD2281 than the other 2 patients in the cohort (C_{max} was 3-4 folds higher and $AUC_{(0-10)}$ was 5-9 folds higher), although there was observed no marked difference of plasma concentration profile and exposure of AZD2281 following single dose, compared with the other 2 patients. The background demographic and laboratory tests data for this patient were generally similar to the other patients. As a result, it was difficult to identify the reason why the exposure of AZD2281 increased markedly by multiple dosing in this patient.

With exception of Patient E0001003, accumulation ratios of $AUC_{(0-10)}$ and C_{max} showed that in general exposure did not increase markedly by twice daily administration of AZD2281 at dose levels of 100 mg bd, 200 mg bd, and 400 mg bd. Temporal change parameters (TCP; $AUC_{(0-12)}$ on Multi Dose Phase Day 15 / AUC following the single dose on Single Dose Phase Day 1) ranged 0.563 to 1.61, with exception of Patient E0001003, suggesting steady state for

AZD2281 had been achieved by twice daily dosing of AZD2281 for 15 days and the time-independent kinetics of AZD2281.

In general, there was observed a less than proportional increase in exposure (in terms of C_{max} and AUC) with increasing dose for both single and multiple dosing. However due to one patient showing higher exposure after multiple dosing (Patient E0001003), it was difficult to clearly conclude the dose-proportionality of the exposure after multiple dosing.

Summary of pharmacodynamic results

The average % inhibition of PARP-1 activity in PBMCs was more than 50% at 6 hours post-dose on Day1 in 100 mg bd,200 mg bd and 400 mg bd groups, and the PARP-1 activity inhibition continued at the same level of inhibition on Day 8 and Day15 during multiple dosing phase at all dose levels.

There was no dose relationship in the PARP inhibitory activity across the investigated dose range (100 mg bd, 200 mg bd, and 400 mg bd).

Decreased PARP activity in PBMCs suggests pharmacological activity could be achieved at clinically well-tolerated doses of the investigational drug (100 mg bd, 200 mg bd and 400 mg bd).

Summary of pharmacokinetic/pharmacodynamic relationships

Any analysis of the relationship between AZD2281 plasma concentration /PK parameters and the extent of PARP-1 inhibition could not be carried out because of the small number of samples.

Summary of safety results

Overall mean actual exposure to study treatment was 90.5 days (range 9 to 436 days).

The number of patients who had at least 1 AE in any category during the course of the study is presented in Table S1

Table S1 Summary of number (%) of patients who had at least 1 AE in any category: safety analysis set

	Number (%) of patients			
	100 mg bd	**200 mg bd**	**400 mg bd**	**Total**
	n=3	**n=3**	**n=6**	**n=12**
Any AE	3 (100.0)	3 (100.0)	6 (100.0)	12 (100.0)
Any causally related AE	3 (100.0)	2 (66.7)	6 (100.0)	11 (91.7)

Table S1 Summary of number (%) of patients who had at least 1 AE in any category: safety analysis set

	Number (%) of patients			
	100 mg bd	**200 mg bd**	**400 mg bd**	**Total**
	n=3	**n=3**	**n=6**	**n=12**
Any AE of CTCAE grade 3	1 (33.3)	0	1 (16.7)	2 (16.7)
Any AE of causally related CTCAE grade 3	1 (33.3)	0	1 (16.7)	2 (16.7)
Any AE leading to discontinuation of study	0	0	0	0
Any other significant AE	0	0	0	0
Any SAE (including outcome = death)	0	0	0	0
Any SAE leading to death	0	0	0	0

* Patients with multiple events in the same category are counted only once in that category. Patients with more than 1 category are counted once in each of those categories.
Data derived from Table 11.3.2.1 and Table 11.3.2.2, Section 11.3

AEs occurring in ≥3 patients across the three dose cohorts were such as nausea (6), blood creatinine increased (4), haematocrit decreased (4), white blood cell count decreased (4), lymphocyte count decreased (4), red blood cell count decreased (3), anorexia (3), hyperglycaemia (3), and anaemia (3). The majority of the events reported in this study were mild to moderate in intensity (CTCAE grade 1 or 2).

Two patients had AEs of CTCAE grade ≥3; 1 patient (100 mg group) had a grade 3 AE of ALT increased, and 1 patient (400 mg group) had a grade 3 AE of anaemia. Both AEs were considered related to AZD2281 by the investigator and resulted in dose reduction and /or dose interruption. Overall, 3 patients had dose interruptions and/or dose reductions due to AEs after DLT evaluation period; 1 patients in 400 mg bd group for dose interruption and dose reduction due to the AE of “Anaemia” and 2 patients in 100 mg bd group and 400 mg bd group for dose interruption due to the AE of “Alanine aminotransferase increased” and “Anaemia”.

The majority of the events reported in this study were mild to moderate in intensity (CTCAE grade 1 or 2). There were no SAE, discontinuations due to AEs or deaths during the trial. There were only 2 AEs ("Anaemia" and "Alanine aminotransferase increased") of CTCAE grade =3 resulting in a dose reduction and/or interruption. There were no other clinically important laboratory findings.