AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ZD4054
Study Code	D4320C00041
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A Phase I, Open-label, Single-arm Study to Determine the Single and Multiple Dose Pharmacokinetics of 10mg ZD4054 Administered Once Daily in Male, Elderly Chinese Patients with Advanced Solid Malignancies

Study dates: First subject enrolled: 20 Oct 2009
Last subject last visit: 21st Sep 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 was an open-label, single-arm study conducted in one site- Department of medical oncology, Shanghai Cancer Hospital, China

Publications

None.

Objectives and criteria for evaluation

The primary objective of this study was to assess the pharmacokinetics of single and multiple doses of 10mg ZD4054 in male, elderly Chinese patients with advanced solid malignancies.

The secondary objective of this study was to assess the safety and tolerability of single and multiple doses of 10mg ZD4054 in male, elderly Chinese patients with advanced solid malignancies.

Study design

This was an open-label, single-arm study to determine the pharmacokinetic profile of 10mg ZD4054 after single and multiple dosing and assess the safety and tolerability of this drug in male, elderly Chinese patients with advanced solid malignancies.

Target subject population and sample size

Male, elderly (>50 years of age), Chinese patients with advanced solid malignancies, at least 3 with prostate cancer. The recruitment continued until at least 12 patients (of whom at least 3 have prostate cancer) who were evaluable for pharmacokinetic analysis had been enrolled into the study.

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

Patients took the ZD4054 tablets with 200 mL of water on Days 1 and 15 and with a glass of water on all other days, and had to consume all the fluid. The tablets had to be swallowed whole and not chewed, crushed or divided.

A dose of 10mg ZD4054 was given on the morning of Day 1, followed by a 72 hour washout period, then 12 days of consecutive morning dosing were given from Days 4 to 15.

ZD4054 packed into white high-density polyethylene (HDPE) bottles with child resistant, tamper evident closures. The batch (ADM) number was as follows: F013466.

Duration of treatment

Part A

Each patient was administrated a dose of 10mg ZD4054 on the morning of Day 1, followed by a 72 hour washout, and then 12 days of consecutive morning dosing were given from Days 4

to 15. At the end of 12 days multiple dosing patients might continue to receive ZD4054 after having discussed with the investigator as long as they were continuing to derive clinical benefit and did not meet any of the criteria for discontinuation. A 28-day safety follow up following Day 15 (i.e. Day 43) was performed.

Part B (beyond Day 43)

Patients might continue to receive ZD4054 at the investigator's discretion as long as they were continuing to derive clinical benefit and did not meet any of the criteria for discontinuation. A 28-day safety follow up following last dosing of ZD4054 were performed.

Statistical methods

No formal statistical analyses were performed in this study. Summary measures of plasma concentrations across time and derived pharmacokinetic parameters were to be produced. Safety and tolerability variables were also summarized.

The main analysis took place when the full data from Part A (i.e. from Day1 to Day 43) were available, subsequent safety assessments continued to be performed until the patient was withdrawn from the medication with ZD4054 (Part B).

Subject population

In total, 16 patients from one center-Shanghai Cancer Hospital, China were enrolled into this open-label, single-arm study (ie, provided informed consent). The first patient was enrolled on 20 Oct 2009, and the last patient was enrolled on 14 Aug 2010. Fifteen patients received study treatment. The data cut-off for this CSR was 25 Oct 2010, at which time 4 (26.7%) patients were ongoing.

The mean age was 64 years. All the patients were male Asian. Three (20%) patients aged between 50-60 years and other majority (73.3%) aged between 60 and 75 years. More patients presented with PS1 (66.7% versus 33.3% for PS0). The most commonly reported primary tumour locations were colon/colorectal/rectal prostate and stomach cancers.

Summary of efficacy results

Summary of pharmacokinetic results

- Following a single oral dose of 10 mg ZD4054 the peak plasma concentrations occurred between 1 and 12 hours post dose, and ranged from 396 ng/mL to 712 ng/mL.

- The apparent clearance and apparent volume of distribution were low and half-life ranged from 4.2 to 17.4 hours. After multiple oral dosing at 10 mg the peak plasma concentrations occurred between 1 and 4 hours post dose, and ranged from 404 ng/mL to 1110 ng/mL. The geometric mean Cmax was higher after multiple dosing compared to single dosing.

- Overall exposure in terms of Gmean AUC was 8138 ng.h/mL after a single dose and AUCss after multiple dosing was 8042 ng.h/mL indicating little temporal change in the pharmacokinetics of ZD4054. The AUCss was higher than the single dose AUC0-24 (6005 ng.h/mL) indicating a small amount of accumulation during multiple dosing.

Summary of pharmacodynamic results (Not applicable)

Summary of pharmacokinetic/pharmacodynamic relationships (Not applicable)

Summary of pharmacogenetic results (Not applicable)

Summary of safety results

- The number (percentage) of patients who experienced one or more adverse events was 10 (66.7%). A total of 6 (40%) patients experienced an adverse event that was considered by the investigator to be related to treatment

- The most frequently reported adverse events were pyrexia (4 [26.7%]), constipation (3 [20.0%]), headache (3 [20.0%]) and oedema peripheral (2 [13.3%]).

- The most commonly reported drug-related adverse events were headache (3 [20.0%]), oedema peripheral (2 [13.3]).

- There were no drug-related CTC Grade 3 or 4 AEs in the study.

- There were no death and SAE other than death in the study.

- A total of 4 (26.7%) patients discontinued due to 6 AEs in the study, which were musculoskeletal Pain, Pyrexia, Gastritis, Headache, Pyrexia, Visual Impairment. Two (13.3%) patients discontinued due to 3 drug-related AEs: gastritis, headache and vision abnormal.

- A slight decrease in Hb (~10 g/L) was observed after IP administration (on Day 15), which returned to baseline levels over time. Most remained within normal ranges and no associated clinical symptoms were observed.

- There were no consistent changes for electrolytes, liver function and renal function.

- There seemed a slight decrease in SBP (systolic blood pressure) concomitant with DBP (diastolic blood pressure) without clinical significance after IP administration (on Day 15), which returned to baseline levels over time. There were no clinically relevant trends in other vital signs, physical finding or ECG observations.