AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

INVESTIGATIONAL PRODUCT: AZD5438

Study No: D0110C00005
A Phase I, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of AZD5438 Given Orally, in 2 Dosing Schedules (4 x Daily Dosing for 28 days or 4 x Daily Dosing for 21 Consecutive Days in a 28 Day Period) in Patients with Advanced Solid Malignancies

Developmental phase: Phase I
Study Completion Date: 7 December 2005
Date of Report: 10 May 2006

OBJECTIVES:

The objectives of the study are shown in Table 1, along with their associated variables.

Table 1 Study objectives and associated variables

Objectives	Variables
Primary	**Primary**
To investigate the safety and tolerability of multiple oral doses of AZD5438 in 2 schedules in patients with advanced solid malignancies	Incidence and severity of adverse events (National Cancer Institute Common Terminology Criteria for adverse events [CTCAE] version 3.0), vital signs, ECG parameters, clinical chemistry, haematology, urinalysis
Secondary	**Secondary**
To investigate the pharmacokinetic (PK) profile of AZD5438 following single and multiple dosing	Single dose PK parameters: maximum plasma concentration (C_{max}), time to reach the C_{max} (t_{max}), area under plasma concentration time curve from zero to 5 h ($AUC_{(0-5)}$), area under plasma concentration time curve from zero to 24 h ($AUC_{(0-24)}$), area under plasma concentration time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$), area under plasma concentration time curve from zero to infinity (AUC), terminal half life ($t_{½}$), plasma clearance following oral dosing (CL/F), volume of distribution at steady state following oral dosing (Vdss/F) Multiple dose parameters: minimum plasma concentration (C_{min}) samples during escalation to steady state, at steady state $C_{max\ ss}$, $t_{max\ ss}$, $C_{min\ ss}$, $AUC_{(0-\tau)}$, $AUC_{(0-t)}$, CLss/F, AUC and $t_{½}$ Explore the 'linearity' of exposure after single dose and at steady state, determine time to achieve steady state, accumulation ratio and

Table 1 Study objectives and associated variables

Objectives	Variables
	predictability of kinetics single to multiple dose
Exploratory	**Exploratory**
To investigate the effects on various biomarkers in normal, non tumour rapidly dividing tissues following multiple, oral doses of AZD5438	Peripheral blood mononucleocyte (PBMC) – levels of biomarkers that may include ^{3}H-thymidine incorporation, phospho histone H3 (pHH3), E2F1 (transcription factor) and cyclins Hair follicles – biomarkers that may include levels of phosphorylated protein p27, phosphorylated pRb, and Ki67
To investigate whether there is any relationship between PK and PD for AZD5438	Graphical display of the PK variables defined in this study (eg, C_{max}, AUC, plasma concentrations) versus PD variables (eg, changes in biomarkers, incidence of AEs)
To obtain a preliminary assessment of anti tumour activity	Tumour response in measurable disease using Response Evaluation Criteria for Solid Tumours (RECIST) Levels of serological markers (eg, prostate specific antigen [PSA], carcino-embryonic antigen [CEA], human chorionic gonadotropin [HCG], alpha feto proteins [AFP], cancer or carbohydrate antigen 125 [CA125] and cancer or carbohydrate antigen 15.3 [CA15.3]) for those patients that have tumours that are associated with these markers
To investigate the pharmacogenetic profile of tumour samples	Mutational analysis of genes involved in the cell cycle pathway or upstream of the cell cycle pathway, eg, p53, p16, p21, p27, K-ras, PTEN from unstained paraffin embedded tumour samples (in patients who consent to such analysis) [These results are not reported in this CSR]
Exploratory (enrichment phase)	**Exploratory (enrichment phase)**
To investigate the effect on various biomarkers of cell cycle progression, cell proliferation and apoptosis in tumour tissue following multiple, oral doses of AZD5438	Variables related to enrichment phase: levels of phosphorylated pRb and phosphorylated p27, total pRb and p27 in tumour tissue; levels of phosphorylated survivin, survivin, cyclin dependent kinase 2 (CDK2), CDK1, E2F1, and pHH3; expression levels of cyclins A, B, D1 and E; measures of apoptosis, including terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TuNeL) and expression of caspase 3; expression of the proliferation marker Ki67 [Since the enrichment phase was not conducted, these results are not reported in this CSR]

A review of the emerging clinical tolerability and exposure data from this study in conjunction with preclinical and the available clinical pharmacodynamic data relating to AZD5438, led to a decision by AstraZeneca that the development of AZD5438 as a potential anti-cancer agent would be discontinued. As a consequence of this decision, this study was prematurely terminated and will be reported in an abbreviated format. Therefore, the protocol objectives outlined in the table below cannot be fully analysed in this report. Available data and analyses are presented in the following results sections for safety and pharmacokinetics.

METHODS:

This was a Phase I, open-label, dose escalation (in 2 dosing schedules) multi-centre study to be conducted in 3 parts (Parts A & B followed by an enrichment phase). However, the

study was terminated early (during Part A) due to emerging safety data in this study and another Scheduling Study (D0110C00004).

Part A: Patients were dosed daily for 28 days. Patients received 1 dose on the first day of the first cycle, then 4 doses per day (QID) on subsequent days. Dose escalation occurred in a new cohort of patients after 3 patients had completed a 28-day treatment cycle, based on pre-defined dose decision criteria. Dose escalation continued until the non-tolerated dose was defined.

Blood samples were collected for 24 h following a single dose on Day 1, at pre-dose and 1.5 h post the first dose on Days 8, 15 and 22, and up to 5 h post the first dose on Day 29, for quantification of plasma AZD5438 concentrations. Blood samples for PBMC analysis, and hair follicle samples for the analysis of activation and proliferation markers, were collected immediately pre first dose and 1.5 h post first dose on Day 1, and 1.5 h post first dose on Day 8.

Part B (not performed): It was planned that the maximum tolerated dose (MTD) from Part A would be used as the starting dose for Part B. Patients were to have been dosed daily for 21 days followed by 7 days of no treatment, with 1 dose on the first day of the first cycle, then 4 doses per day on subsequent days. Dose escalation was to occur in a new cohort of patients after 3 patients had completed a 28-day treatment cycle, based on pre-defined dose decision criteria. Dose escalation was to be continued until the non-tolerated dose was defined.

Enrichment phase (not performed): It was planned that once the MTD had been defined in Parts A and B, between 12 and 20 patients would be recruited to provide additional safety, tolerability and pharmacodynamic data to ensure that there were 12 patients with 2 evaluable tumour samplings, one pre-dose and one post-dose. Patients were to have been randomised in a 1:1 ratio to the MTD from Part A or B and follow the corresponding dose schedule.

Duration of treatment

Part A: During Part A, AZD5438 was administered QID for 28 days (excluding Day 1 of the first cycle when a single dose was given).

Patients continued on the same dose and schedule providing they did not meet any pre-defined discontinuation criteria and continued to receive benefit. If dose-limiting toxicity was encountered, the patient's treatment was stopped until resolution of the toxicity. At the discretion of the Investigator, treatment could be restarted at the next lowest well tolerated dose in patients who had not developed progressive disease.

AZD5438 dose escalations occurred as per protocol. The top dose of AZD5438 investigated was 40 mg QID. .

Statistical methods

No formal statistical analysis was performed. All data are listed and, where appropriate, summarised.

RESULTS:

Patient population

In total, 28 patients, 18 (64%) male and 10 (36%) female, with advanced solid malignant tumours were confirmed as eligible for the study and assigned a study number (the first patient was enrolled on 14 July 2004, and the last patient completed the study on 7 December 2005). Twenty-six (92.9%) patients were Caucasian, 1 (3.6%) patient was Black and 1 (3.6%) patients was Asian (non-Japanese). The mean (SD) age of the patients was 58.3 (13.1) years (range 33 to 84).

In the 10 mg cohort, the main reason for discontinuation was disease progression (n=2). At 20 mg, the main reasons for discontinuation were disease progression (n=2), withdrawal of consent (n=3) and adverse events (n=2, [Patient 13: anorexia and Patient 16: myocardial infarction/hypoxia/hyponatraemia]). At 40 mg, the main reasons for discontinuation were withdrawal of consent (n=2) and adverse events (n=2, [Patient 26: pericarditis and Patient 28: fatigue/dyspnoea]).

All 15 patients who completed the first dose cycle were later discontinued from the study. The main reason for discontinuation was disease progression (n=13). Of the remaining 2 patients, 1 patient withdrew consent (Patient 10 at 10 mg), and the other patient was discontinued at the Investigator's discretion (Patient 25 at 40 mg).

Safety results

In this study, repeat daily doses of AZD5438 (QID) were administered in ascending doses ranging from 2.5 mg QID to 40 mg QID.

Twenty-seven patients reported a total of 166 AEs during the study. Eight patients reported a total of 12 serious adverse events (SAEs) during this study, including 2 deaths. One other patient died due to disease progression.

Table 2 Number of patients who had at least 1 treatment-emergent adverse event in any category, and total numbers of AEs

Category of adverse event	AZD5438					
	2.5 mg QID n=3	5 mg QID n=3	10 mg QID n=5	20 mg QID n=11	40 mg QID n=6	Total n=28
	N of patients who had an adverse event in each category[a]					
Any adverse events	2	3	5	11	6	27
Treatment related adverse events	1	1	4	5	5	16
Serious adverse events	0	1	2	3	2	8
Deaths	0	0	0	1	1	2
Discontinuations of study drug due to adverse events	0	0	2	2	3	7
Treatment related adverse events leading to discontinuation	0	0	1	0	2	3
	Total number of adverse events					
Adverse events	11	12	38	60	45	166
Treatment related adverse events	4	2	7	17	24	54
Serious adverse events	0	1	5	4	2	12

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories. In addition, AEs that emerged before the start of study drug were not summarised.

Overall, the most frequently reported AEs were within the gastrointestinal disorders system organ class (SOC). Of these, the number of patients reporting AEs (preferred term) in each cohort appeared to increase in a dose-dependent manner.

There were no clinically important findings relating to haematological, clinical chemistry, urinalysis, vital signs, or ECG parameters, except for elevation of white cell counts in Patient 26 who experienced a fatal SAE (pericarditis).

AZD5438 40 mg QID administered on a daily basis was delineated as a non-tolerated dose. The DLTs were fatigue and circulatory collapse due to pericarditis. The latter event was associated with a prodrome of worsening nausea, vomiting and lethargy. Due to premature termination of the study, the MTD was not established.

Pharmacokinetic results

Following administration of single oral doses to patients (ie, following dosing on Day 1 of the study), absorption of AZD5438 was rapid with maximum plasma concentrations achieved between 0.5 and 3 h after dosing. There was no evidence of any change in t_{max} as administered dose increased. Beyond the peak, plasma concentrations in all patients declined rapidly over the time period studied (up to 24 h after dose administration) but it was not possible to adequately define that decline in 2 of the 28 patients dosed. Consequently, $t_{½}$, AUC, CL/F and Vss/F could not be reported for Patients 5 (5 mg dose) or 16 (20 mg dose). In the 26 remaining patients, with one exception where it accounted for 22%, the percentage of the AUC extrapolated beyond

the last data point was <20% and the $t_{½}$ of the terminal phase for the majority of patients fell between 1 and 4 h. Longer half lives (7.24, 4.36, 5.28, 8.09, 4.44, and 7.61 h) were seen in 6 of the patients dosed (at the 5, 10, 10, 20, 40 and 40mg doses, respectively) and in addition, although an actual value could not be reported due to the limitations of the data collected, the terminal half life observed in a further patient at the 20 mg dose level (Patient 16) was of the order of 12 h.