AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8931
Study Code	D0102C00002
Edition Number	1
Date	15 June 2010

A Phase I, Open-label, Multiple-dose, Dose-escalation Study To Assess the Safety, Tolerability and Pharmacokinetics of AZD8931 in Patients with Advanced Solid Malignancies

Study dates: First patient enrolled: 22 February 2008
Last patient enrolled: 26 May 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 conducted at 5 centres in Germany and Russia.

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	Type
Primary	**Primary**	
To explore the safety and tolerability of multiple ascending doses of AZD8931 in patients with advanced solid malignancies	Adverse events, laboratory findings, physical examinations, vital signs, cardiac monitoring, dermatological examinations and ophthalmological examinations	Safety
Secondary	**Secondary**	
To identify MTD of AZD8931 following repeated twice daily administration	Dose-limiting toxicities	Safety
To explore the PK of single doses of AZD8931 in patients with advanced solid malignancies	AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, AUC, C_{max}, t_{max}, $t_{½}$, CL/F and V/F	PK
To explore the PK of multiple doses of AZD8931 in patients with advanced solid malignancies	$AUC_{ss,0-12}$, $C_{ss,max}$, $t_{ss,max}$, CL_{ss}/F, $C_{ss,min}$, R_{AC} and linearity factor	PK
Exploratory	**Exploratory**	
To measure cell death biomarkers from blood samples to examine the relationship to treatment with AZD8931 (optional)[a]	Correlation of cell death (proapoptotic) biomarkers with AZD8931 therapy (optional)	Biomarkers
To obtain a blood sample for host pharmacogenetics for DNA extraction and archiving (optional)[a]	Pharmacogenetic sampling (blood sample) for DNA extraction and archiving (optional)	Pharmaco-genetics

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Exploratory	**Exploratory**	
To obtain preliminary assessments of the efficacy of AZD8931 (including RECIST criteria and change in tumour length)	ORR and best overall response (based on RECIST) for patients with measurable disease, or other measures of efficacy in patients with non-measurable disease	Efficacy

[a] Reported separately from the CSR.

AUC: Area under the plasma concentration-time curve from time zero to infinity; AUC_{0-12}: Area under the plasma concentration-time curve from time zero to 12 hours; AUC_{0-24}: Area under the plasma concentration-time curve from time zero to 24 hours; AUC_{0-t}: Area under the plasma concentration-time curve from time zero to time t; $AUC_{ss,0-12}$: Area under the plasma concentration-time curve from time zero to 12 hours at steady state; CL/F: Total apparent drug clearance; CL_{ss}/F: Total apparent drug clearance at steady state; C_{max}: Maximum plasma concentration; CSP: Clinical study protocol; $C_{ss,max}$: Maximum plasma concentration at steady state; $C_{ss,min}$: Minimum plasma concentration at steady state; MTD: Maximum tolerated dose; ORR: Objective response rate; PK: Pharmacokinetics; R_{AC}: Accumulation ratio; RECIST: Response Evaluation Criteria in Solid Tumours; SAP: Statistical analysis plan; ss: Steady-state; $t_{½}$: Terminal elimination half-life; t_{max}: Time to reach maximum plasma concentration; $t_{ss,max}$: Time to reach maximum plasma concentration at steady state; V/F: Apparent volume of distribution.

Study design

This was a Phase I, open label, multiple-dose, dose-escalation study to assess the safety, tolerability and pharmacokinetics (PK) of AZD8931 in patients with advanced solid malignancies. In each dose cohort, each patient received initial treatment with a single dose of AZD8931, followed by a 4-day observation period then a 21-day repeat dosing treatment period with twice daily dosing starting between Study Days 5 and 7 (repeat dosing Days [R] 1 to R21).

After each dose cohort, the safety monitoring committee (SMC) evaluated the safety, tolerability and the PK of AZD8931 and decided the next dose (planned dose, increased or decreased dose, repeated dose or dose stopped). The dose was initially escalated by dose-doubling, up to a level where the SMC decided that smaller escalation steps were warranted.

Target patient population and sample size

Adult male and non-pregnant female patients with advanced solid malignancies were eligible for enrolment into this study. Patients were required to have a histologically or cytologically confirmed solid, malignant tumour, cancer refractory to standard therapies, or for which no standard therapies exist, and a World Health Organisation (WHO) performance status 0 to 2.

The study was to be conducted in approximately 30 patients. A minimum of 3 and a maximum of 6 evaluable patients were recruited in each cohort. If there was a dose limiting toxicity (DLT) in 1 of the initial 3 patents, a cohort would be expanded to 6 evaluable patients. In total, 40 patients were enrolled, 28 patients were treated and 21 patients were evaluable across 5 dose cohorts.

Investigational product: dosage, mode of administration and batch numbers

AZD8931 tablets (10 mg [batch numbers 40759I06 and 51732B07], 40 mg [batch numbers 33233B05, 51733J07 and 60694J08] and 100 mg [batch numbers 51734G07 and 53285F07]) were administered orally.

The initial dose level was 40 mg twice daily (except for the single dose on Study Day 1) and doses were taken approximately 12 hours apart.

Duration of treatment

The initial treatment of a single dose of AZD8931 40 mg was followed by a 4-day observation period and a 21-day treatment period with twice daily dosing starting between Study Days 5 and Day 7. Patients continued treatment after Day R21 if, in the investigator's opinion, the patient was receiving or might receive some benefit from therapy, was free from intolerable toxicity and had not met a discontinuation criterion.

Statistical methods

No formal statistical analysis was performed. The data were summarised using descriptive statistics, and where appropriate, graphical displays.

Three patient analysis sets were used in the study; the safety set, the dose escalation evaluable set and the PK evaluable set.

Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities Version 12.0. For all safety assessments (eg, laboratory assessments, vital signs), the baseline value was defined as the last available measurement prior to the first dose of AZD8931. Adverse events were graded using Version 3 of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

Patient population

In total, 40 patients were enrolled into the study (informed consent received) at 5 study centres, of whom 28 patients received at least 1 dose of study treatment. All 28 patients started the dose escalation evaluation period; 22 patients completed the 21-day period; and 9 patients continued treatment after Day R21. The most common reason for discontinuation of treatment during the dose escalation evaluation period (Days R1 to R21) and after Day R21 was: AE (5 patients) and worsening of the condition under investigation (5 patients), respectively. The most common reason for patients stopping treatment at Day R21 was the continuation of treatment being considered optional (9 patients).

All 28 patients were included in the safety analysis set and in the PK evaluable set. In total, 7 patients (25.0%) were excluded from the dose escalation evaluable set; failed exclusion criteria and interruption of AZD8931 for an AE that was not optimally treated were the only reasons for exclusion reported for more than 1 patient overall.

The demographic and baseline characteristics of the cohorts were generally comparable. The overall mean age was 55.6 years, with a majority of patients aged from 50 to 70 years. The primary tumour site varied but the most commonly reported sites were ovary (8 patients [28.6%]) and breast (5 patients [17.9%]). Medical and surgical history, and physical examination findings were as expected for a population of patients with advanced cancer.

Table S2 Summary of patient disposition

Disposition	Number (%) of patients					
	AZD8931 40 mg bd (N=5)	AZD8931 80 mg bd (N=8)	AZD8931 160 mg bd (N=6)	AZD8931 240 mg bd (N=6)	AZD8931 300 mg bd (N=3)	Total (N=40)[a]
Patients who received treatment[b]	5 (100.0)	8 (100.0)	6 (100.0)	6 (100.0)	3 (100.0)	28 (70.0)
Patients who started repeat treatment	5 (100.0)	8 (100.0)	6 (100.0)	6 (100.0)	3 (100.0)	28 (70.0)
Patients who completed the 21-day evaluation period	4 (80.0)	6 (75.0)	4 (66.7)	6 (100.0)	2[d] (66.7)	22 (55.0)
Patients who continued treatment after Day R21	1 (20.0)	1 (12.5)	2 (33.3)	3 (50.0)	2 (66.7)	9 (22.5)
Patients who continued treatment after data cut-off[c]	0	0	0	0	2 (66.7)	2 (5.0)

[a] Percentage values for these data were calculated out of the number of patients who were enrolled in the study (40 patients).
[b] Patients who received at least one dose of treatment.
[c] Data cut-off is 18 June 2009.
[d] Both patients reduced their dose during the period after the dose was declared non-tolerable.
R#: Repeat dosing day (number).
Note: AZD8931 was dosed twice daily (bd) except at Day 1.

Summary of efficacy results (exploratory objective)

No complete or partial responses were reported for any patient during the study, at Day R21 the majority of patients had stable disease (57.1% of patients); progression of disease was observed in 42.9% of patients in this Phase I study. Five patients had a reduction in target lesions, of which 3 patients had concurrent progression of non-target/new lesions. Only 4 patients had tumour assessments beyond Day R21. It should be noted that follow up was only for 3 weeks in the majority of patients, which is likely to have been too short a timeframe to see responses in patients with stable disease; only 4 patients had scans after the 3-week follow up.

Summary of pharmacokinetic results (secondary objectives)

- After single and multiple doses of AZD8931, absorption was rapid with a median time to maximum plasma concentration (t_{max}) achieved between 1 and 3 hours in the fasted state.

- Following maximum plasma concentrations (C_{max}), the distribution was biphasic with a mean terminal elimination half-life ($t_{½}$) of approximately 11 hours. Given an 11 hour $t_{½}$, steady state was predicted to occur by Day R3 and accumulation to be 1.9-fold.

- Following twice daily dosing, steady state was achieved by Day R2

- Mean accumulation was approximately 1.5-fold.

- The mean linearity factor was approximately 1 for all dose levels investigated, indicating that there were no time-dependent changes in PK upon multiple dosing of AZD8931 to Day R14.

- AZD8931 is a moderate to high clearance drug. Total apparent drug plasma clearance (CL/F) of AZD8931 remained approximately constant across the dose range of 40 mg to 160 mg AZD8931, the mean ranged from 58.89 to 73.24 L/h, (range: 31.2 to 171 L/h). Total apparent drug clearance at steady state (CLss/F) was on average 50 L/h across the dose range of 40 to 240 mg AZD8931.

- AZD8931 was well distributed in the tissues, as evidenced by the apparent volume of distribution (V/F) being greater than total body water (40 L) and appearing to be independent of dose.

- Following single and multiple dosing, exposure appeared to increase approximately proportionally with doses up to 160 mg; for single doses above 160 mg, exposure increased slightly greater than proportionally with dose.

Summary of safety results

All patients had at least 1 AE; 144 of the 198 AEs reported were considered by the investigator to be related to AZD8931. Overall, 2 patients (7.1%) had a total of 3 serious adverse events, 6 patients (21.4%) had a total of 7 AEs that led to discontinuation of study treatment and 18 patients (64.3%) had a total of 31 CTCAE Grade 3 or 4 events. The frequency of CTCAE Grade 3 or 4 AEs considered by the investigator to be related to AZD8931 increased with increasing AZD8931 dose. No AEs with an outcome of death were reported during the study. Two patients in the 160 mg cohort died during the study due to disease progression.

As expected from the known profile of epidermal growth factor receptor type 1 tyrosine kinase inhibitors, skin-type AEs (specifically acne), diarrhoea and stomatitis were the most commonly reported AEs. Skin-type AEs were reported for 27 of the 28 patients (96.4%) who received AZD8931; acne-type (papulopustular) rashes were the most commonly reported skin-type events (71.4% of patients). All rashes reported for patients in the 40 mg cohort (all of which were acne-type rashes at this dose) were mild (CTCAE Grade 1); there was no clear dose relationship with severity at AZD8931 doses of ≥80 mg twice daily. However, onset of rash occurred earlier for patients on higher doses of AZD8931, particularly for patients

receiving either 240 mg twice daily or 300 mg twice daily. In total, AEs consistent with dry skin or desquamation were reported for 42.9% of patients; there was no clear relationship between AZD8931 dose and the frequency of these skin-type AEs. A total of 6 patients had CTCAE Grade 3 skin-type AEs during the study. Diarrhoea was reported for 75.0% of patients, with incidence and severity increasing with increasing dose of AZD8931. Stomatitis was reported for 28.6% of patients and was recorded as mild (CTCAE Grade 1) in the majority of cases; the incidence of stomatitis was found to increase with dose.

Ophthalmic assessments were conducted routinely during the study. Eye-type AEs were reported in 50% of patients and were mainly mild, resolved without treatment and were not of clinical concern. Although post-baseline changes in ophthalmic assessments were seen during the study, these were generally minor. A reduction in visual acuity of at least 2 levels on the visual acuity chart was recorded in 2 patients receiving AZD8931 240 mg twice daily but these reductions could be explained by concurrent AEs or the patients' medical history. In addition, the 4 patients with findings on Schirmer's test and tear-film break up time did not report subjective symptoms of dry eyes. Thus expert opinion does not consider any of these ophthalmological findings to be of clinical concern in this population of patients with advanced cancer.

There were no findings of clinical concern in vital signs or electrocardiograms, and there was no evidence of an adverse effect of AZD8931 on cardiac function. The haematology and liver biochemistry parameters of the patients in the study were consistent with those expected in patients with advanced cancer. Six patients had newly developed proteinuria during treatment with AZD8931; there was no apparent dose relationship and no specific interventions were required. Small increases in creatinine were observed, which were mainly apparent at AZD8931 doses of 160 mg twice daily and above, and were without any clear correlation to the on-treatment development of proteinuria. Raised creatinine levels could be related to diarrhoea-associated fluid depletion and a clear relationship was observed in the 1 patient (Patient E2001015) who had life-threatening (CTCAE Grade 4) diarrhoea. Other mechanisms that could possibly account for the raised creatinine levels include: inhibition of glomerular filtration or tubular secretory processes, or increased creatinine production. Although some individual increases in plasma glucose values were seen, no overall trend was observed and no fasting glucose samples were recorded, which would have given a more accurate indication of patient glucose levels. No other trends were seen in any of the other clinical chemistry parameters recorded.

Overall, mean actual exposure was 34.7 days with a mean total exposure of 41.0 days. Mean actual exposure (total exposure) ranged from 14.2 days (22.8 days) in the 300 mg cohort to 52.0 days (66.4 days) in the 240 mg cohort. Exposure will have been affected by the fact that in some instances continuation of treatment after Cycle 1 was considered to be optional, which led to many patients being discontinued at Day R21.

In total, 3 DLTs were reported during the study: 1 DLT of rash in the 240 mg cohort and 2 DLTs of diarrhoea in the 300 mg cohort. Based on the protocol definition, the 2 DLTs in the 300 mg cohort meant that this dose was not considered to be tolerated. Therefore,

AZD8931 240 mg twice daily was declared the maximum tolerated dose (MTD) in this study per protocol. However, the incidence and severity of AEs, particularly skin-type events and diarrhoea, reported at AZD8931 doses of 80 mg twice daily and above suggested that long-term administration of AZD8931 at doses above 40 mg twice daily would not be clinically feasible.