Abbreviated Clinical Study Report Synopsis

Drug Substance AZD1152

Study Code D1531C00003

Edition Number 1

A Phase I, Open-Label, Multi-centre Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD1152 Given as a 7-day Intravenous Infusion in Patients With Advanced Solid Malignancies

Study dates: First patient enrolled: 08 August 2006
Last patient completed: 31 July 2007

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 conducted in 3 centres in the United Kingdom. The study was temporarily halted in July 2007 following reports of technical difficulties with infusions; AstraZeneca have not been able to replicate these findings under clinically relevant conditions. The infusion problems observed in this study are thought to be isolated incidents related to conditions encountered in standard clinical practice. A decision was taken in February 2008 not to re-commence this study.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to investigate the safety and tolerability of AZD1152 when given as a continuous 7-day infusion every 21 days in patients with solid malignancies.

The secondary objectives of the study were:

- To determine the pharmacokinetics (PK) of AZD1152 hydroxy-quinazoline pyrazole anilide (AZD1152 hPQA), and if possible AZD1152, from the observed concentration-time profiles
- To explore the effect of AZD1152 on biomarkers of Aurora kinase activity
- To explore the relationship between plasma exposure of AZD1152 hQPA and AZD1152 and effects on biomarkers and/or safety parameters
- To obtain a preliminary assessment of AZD1152 anti-tumour activity
- To determine the preliminary anti-tumour activity of AZD1152 in patients by assessment with 2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) after Cycle 1 compared to baseline.

Tertiary objectives were:

- Assessment of the effects of AZD1152 on tumours by measuring phospho-histone H3 staining in mitotic figures and other markers of tumour activity, such as: proliferative marker Ki67; apoptotic markers cleaved caspase 3 and M30; DNA ploidy in tumour. In addition, assessment of the effects of AZD1152 on markers in blood, such as: M30; M65; number of circulating tumour cells (CTCs); and DNA content in CTCs.
- To investigate whether any variability in the PK, safety, efficacy or pharmacodynamic results could possibly be explained by differences in the patient's

genotype, including tumour related somatic mutation, or phenotype (eg, Aurora kinase A or B expression).

Study design

This was an open label, 2-part, multi-centre, Phase I, dose ascending study, designed to determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of AZD1152 when administered as a continuous 7-day intravenous (IV) infusion once every 3 weeks to patients with advanced solid malignancies. The study was also designed to characterise the safety, tolerability, biological activity and PK profile of AZD1152 (and AZD1152 hQPA) when administered under this schedule.

The study was to be conducted in 2 parts:

- A Dose Escalation Phase: Patients received a continuous 7-day IV infusion of AZD1152 repeated every 3 weeks (7 days treatment followed by 14 days off treatment). A modified accelerated titration design was used for dose escalation. The starting dose was AZD1152 50 mg (total dose) over 7 days (based on pre-clinical data) in 1 patient. The minimum number of patients per dose level became 3 following the first occurrence of a Common Terminology Criteria for Adverse Events Grade 2 or worse treatment-related toxicity. If a DLT occurred in a single patient cohort, the cohort for that dose was to be expanded up to a maximum of 6 evaluable patients. Successive cohorts of patients were permitted to receive escalating doses of AZD1152 until the non-tolerated dose was reached.

- A Safety Expansion Phase: Up to 15 patients were to receive the schedule defined in the dose escalation phase at the MTD to further evaluate the safety, tolerability, biological activity and PK following dosing of AZD1152. Patients entering the safety expansion phase were to have the option to provide tumour biopsies.

Eligible patients were also to undergo a FDG-PET assessment during the study; the FDG-PET assessment was optional for patients in the dose escalation phase. However, no FDG-PET assessments were performed.

Recruitment into the study was temporarily halted in July 2007 following reports of technical difficulties relating to the continuous 7-day infusion of AZD1152 in patients with advanced solid tumors. Two central venous catheters were sent to AstraZeneca for investigation following reports that they had become blocked during or following infusion of AZD1152. In subsequent investigations, AstraZeneca has been unable to replicate the infusion problems under clinically relevant conditions. No reports of infusion problems have been reported in patients treated with shorter infusions or in other studies which use the same 7-day continuous infusion schedule. This suggests that the infusion problems observed in this study were isolated incidents related to conditions encountered in standard clinical practice. A decision was taken in February 2008 not to re-commence this study.

Target healthy volunteer population and sample size

Male or female patients aged 18 years or over, who were likely to survive for ≥3 months, with histological or cytological confirmation of a solid malignant tumour, which was refractory to standard therapies, for which no standard therapies exist, or for which the investigator felt no other active therapy was required for the duration of the study (inclusion was irrespective of stage of disease).

There was no formal sample size calculation. This study was expected to recruit 30 to 60 patients, recruited from up to 4 centres in the United Kingdom. The actual number of patients to be recruited however was dependent on the number of dose escalation steps within the study. For the safety expansion phase, the target number of patients with evaluable FDG-PET assessments (baseline and follow-up) was 10. Taking into account that some tumours might not be suitable for FDG-PET assessment, it was anticipated that up to 15 patients would be recruited, in order to achieve a minimum of 10 patients with evaluable FDG-PET data.

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

AZD1152 was formulated as a 100 mg lyophile and supplied in 10 ml vials together with a 5 ml diluent for reconstitution of the lyophile for preparation for IV infusion. The required volume of concentrate was further diluted in commercially available 0.9% sodium chloride injection prior to administration as an IV infusion.

The starting dose for the 7-day (168 hours) continuous dosing schedule was approximately 50 mg as a total dose over the 7 days. Dose escalation occurred once each cohort of patient(s) had completed the first treatment cycle. Two batches of AZD1152 100 mg (Batch numbers: 32929D05 and 43746A06) and 1 batch of diluent (Batch number: 33317D05) were used in this study.

Duration of treatment

Each patient was administered a continuous 7-day infusion of AZD1152 given every 3 weeks. Patients could continue treatment with AZD1152 provided that the investigator considered that the patient was receiving benefit from treatment.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

The secondary outcome variables were:

- Non-compartmental PK parameters which were to be derived for AZD1152 hQPA, and where possible for AZD1152, from the AZD1152 hQPA and AZD1152 concentration-time profiles. Additional compartmental analysis was to be undertaken if warranted by the data.

- Biomarkers of Aurora kinase activity

- Evaluation of tumour response using RECIST (for patients enrolled with measurable disease) and/or measurement of serological markers, if applicable.

- To investigate possible relationships between systemic drug concentrations/exposure and changes in pharmacodynamics (PD) and/or safety, using a graphical approach and/or appropriate PK/PD modelling techniques, if the data were suitable.

- FDG-PET standard uptake value averaged over a maximum of 5 lesions, defined as those lesions with highest 2-fluoro-2-deoxy-D-glucose uptake at base-line (the same lesions were assessed at baseline and follow-up).

Criteria for evaluation - safety (main variables)

The primary outcome variable was safety assessed by incidence and severity of adverse events (AEs), vital signs, electrocardiogram parameters, clinical chemistry (including liver function tests), haematology (including coagulation parameters) and urinalysis.

Statistical methods

No formal statistical analyses were performed on the data from this study. PD data were to be summarised descriptively using confidence intervals if sufficient data were collected. However, as this study was terminated early this was not performed. All data (including available PD data) were listed and summarised and in addition, where appropriate, graphical presentations were produced to aid interpretation of the data.

Subject population

- A total of 14 patients were enrolled in the dose escalation phase (ie, informed consent was received) and 14 patients received AZD1152 in the dose escalation phase.

- Seven patients received the AZD1152 50 mg dose. The first patient enrolled was ineligible for consideration in the SRC review of dosing. The second patient enrolled, had a DLT of Grade 3 diarrhoea and was withdrawn from treatment. In accordance with the protocol the cohort was immediately expanded to include 6 evaluable patients. At the next dose of AZD1152, 75 mg, no DLTs were observed in the 3 patients enrolled and the dose was increased to AZD1152 100 mg. Four patients were enrolled in the AZD1152 100 mg cohort, 1 patient in the 100 mg did not receive at least 80% of the specified dose in Cycle 1 and was not considered evaluable for dose escalation and non tolerated dose determination. A replacement patient was enrolled so the minimum number of 3 patients required was met.

- All 14 patients discontinued from the dose escalation phase of this study. The majority of patients (11 patients) discontinued due to a worsening of their condition. Two patients discontinued due to an AE; 1 patient due to an event of catheter related complication and 1 patient due to events of diarrhoea, hyperhidrosis, and vomiting. One patient voluntarily discontinued following a catheter-related infection.

- Inclusion of 1 patient was identified as a major deviation. This patient received radiotherapy 20 days prior to treatment with AZD1152 to a non-target lesion. This patient was not excluded from any data summaries, listings or graphical displays.

- All patients had received previous chemotherapy. Six of the 14 patients had received 3 or more previous chemotherapy regimens. Three of the 14 patients had received previous radiotherapy; no patients had received previous hormonal therapy.

- The most common tumour types were those of the skin/soft tissue (all melanoma, 3 of the 14 patients) and oesophagus (2 of the 14 patients).

Summary of efficacy results

Objective tumour response was evaluated according to RECIST.

- None of the 14 patients in the dose escalation phase of the study experienced a complete response (CR) or partial response (PR) according to RECIST.
  Two patients (1 patient in the AZD1152 50 mg group and 1 patient in the AZD1152 100 mg group) experienced stable disease.

- Seven of the 14 patients experienced disease progression.

- Four of the 5 patients that were classed as not evaluable for RECIST had no post baseline assessments and 1 patient had no baseline RECIST data.

- There was no evidence of anti-tumour activity.

- Few patients had sufficient data for biomarkers to be summarised or explored.

- No FDG-PET assessments were performed.

Summary of pharmacokinetic results

During the infusion phase, plasma concentrations of AZD1152 hQPA were between 2-fold and 8-fold higher (based on maximum plasma concentration [C_{max}] values) than those for AZD1152. Plasma concentrations of AZD1152 were below the limit of quantification of 0.25 ng/mL between 15 minutes and 2 hours post the end of the infusion; whilst AZD1152 hQPA showed a biphasic disposition with low but quantifiable plasma concentrations ranging from 0.347 ng/mL to 1.48 ng/mL up to 24 hours post the end of the infusion. There was an increase in both area under plasma concentration-time curve from zero to time t and C_{max}, of AZD1152 hQPA with increasing dose of AZD1152 although with overlap between the AZD1152 75 mg and 100 mg dose levels. The minimal PK data did not allow interpretation at this time.

Summary of safety results

- This study was stopped early and the MTD of AZD1152 was not determined. No patients were enrolled in the safety expansion phase.

- At the doses used in this study, no new safety concerns were identified from the safety data of the 14 patients enrolled in the dose escalation phase of this study. One DLT was observed at the 50 mg dose (Grade 3 diarrhoea), which led to an expansion of that cohort as per the protocol; no further DLT events were observed at the 2 higher doses (AZD1152 75 mg and 100 mg).

- The most frequent AEs were vomiting, nausea, abdominal pain, fatigue and headache. The majority of AEs were Grade 1 or Grade 2 in toxicity.

- Five of the 14 patients had a serious adverse event (SAE) during the study. Catheter related events were reported in 4 patients; catheter related infection in 2 patients, and catheter line infection and catheter site infection were each reported in a single patient. The patient with catheter site infection also had an SAE of lower respiratory tract infection. Diarrhoea was reported for 1 patient. These patients were not neutropenic.

- Three of the 14 patients permanently discontinued treatment with AZD1152 due to an AE; catheter related infection (1 patient), catheter related infection (1 patient), and diarrhoea, hyperhidrosis and vomiting (all 3 events in 1 patient). The events of catheter related complication, diarrhoea, hyperhidrosis and vomiting were considered by the investigator to be related to AZD1152.

- There were no deaths resulting from AEs or other significant AEs during the study period.

- Based on the available data no clinically relevant trends were observed in the laboratory data.

- No clinically important changes in vital signs or electrocardiograms were observed.