AstraZeneca

Abbreviated Clinical Study Report Synopsis

Drug Substance	AZD1152
Study Code	D1531C00002
Edition Number	1
Date	23 October 2009

A Phase I, Open-Label, Multi-centre Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD1152 Given as 2-hour or 48-hour Intravenous Infusions in Patients With Advanced Solid Malignancies

Study dates: First patient enrolled: 23 May 2006
Last patient completed: 11 March 2008

Phase of development: Clinical Pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

This study was conducted at 2 centres in the United States. The first patient was enrolled into this study on 23 May 2006; the data cut-off for this study was 11 March 2008.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objective	Outcome variables
Primary	
The primary objective of this study was to investigate the safety and tolerability of AZD1152 when given as a continuous 48-hour infusion every 14 days and as a 2-hour IV infusion on 2 consecutive days every 14 days in patients with solid malignancies[a], by assessment of the incidence and severity of AEs (CTCAE, Version 3.0), vital signs, ECG parameters, clinical chemistry (including liver function tests), haematology (including coagulation parameters) and urinalysis.	Incidence and severity of AEs, vital signs, ECG parameters, clinical chemistry (including liver function tests), haematology (including coagulation parameters) and urinalysis.
Secondary	
To determine the PK of AZD1152 hQPA, and if possible AZD1152, from the observed concentration-time profiles.	Non-compartmental PK parameters 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.
To explore the effect of AZD1152 on biomarkers of Aurora kinase activity, by assessment of PD parameters. The biomarkers could include those listed in the CSP (and other markers, depending on emerging data from translational research).[b]	Summary of biomarker levels and change in biomarker levels, by dose and by time.
To explore the relationship between plasma exposure of AZD1152 hQPA and AZD1152 and effects on biomarkers and/or safety parameters. This was to be assessed using a graphical approach and appropriate modelling techniques.[b]	If the data were suitable, investigation using a graphical approach and/or appropriate PK/PD modelling techniques, of possible relationships between systemic drug concentrations/exposure and changes in PD and/or safety parameters.
To obtain, if the data were suitable, a preliminary assessment of AZD1152 anti-tumour activity, by evaluation of tumour response using RECIST criteria (for patients enrolled with measurable disease) [c] and/or measurement of serological biomarkers (eg, CEA, PSA), if applicable[d].	Evaluation of tumour response using RECIST (for patients enrolled with measurable disease) and/or measurement of serological markers for those patients enrolled with non-measurable tumours that had serological markers.

Table S1 Primary and secondary objectives and outcome variables

Objective	Outcome variables
To determine the preliminary anti-tumour activity of AZD1152 in patients by assessment with FDG-PET (or FDG-PET/computed tomography) after Cycle 1 compared to baseline.	Analysis of the FDG-PET standard uptake value from baseline to post-dose. The standard uptake value was to be averaged over a maximum of 5 lesions, defined as those lesions with highest 2-fluoro-2-deoxy-D-glucose uptake (the same lesions were assessed at baseline and follow-up).

[a] To clarify patients received AZD1152 as a continuous 48-hour IV infusion every 14 days or a 2-hour IV infusion on 2 consecutive days every 14 days.
[b] This objective was not met as limited data were available on a small number of patients, which did not allow these data to be summarised or explored further.
[c] Assessment of anti-tumour activity by RECIST was performed for patients enrolled with measurable disease only.
[d] Analysis of anti-tumour activity using serological biomarkers was not performed as limited data were available on a small number of patients, which did not allow these data to be summarised or explored further.

Note: There were 4 tertiary (exploratory) objectives in the study (PD and genetic analyses), none of which are presented in the main study report.

AE Adverse event; AZD1152 hQPA AZD1152 hydroxy-quinazoline pyrazole anilide; CEA Carcinoembryonic antigen; CTCAE Common terminology criteria for adverse events; ECG Electrocardiogram; FDG-PET 2-fluoro-2-deoxy-D-glucose-positron emission tomography; PD Pharmacodynamic; PK Pharmacokinetic; PSA Prostate-specific antigen; RECIST Response Evaluation Criteria In Solid Tumours.

Study design

This was an open label, 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 48-hour intravenous (IV) infusion once every 14 days or as a 2-hour IV infusion for 2 consecutive days every 14 days to patients with advanced solid malignancies. The study was also designed to characterise the safety, tolerability, biological activity, and pharmacokinetic (PK) profile of AZD1152 and AZD1152 hydroxy-quinazoline pyrazole anilide (AZD1152 hQPA) when administered under this schedule.

Two dosing schedules were to be evaluated in this study; initially in a dose escalation phase to determine the MTD for each schedule (Part A and Part B) followed by a safety expansion phase (Part C).

- A dose escalation phase using a 48-hour IV infusion of AZD1152 (Part A): Patients received a continuous 48-hour IV infusion of AZD1152 repeated every 14 days (2 days treatment followed by 12 days off treatment). The starting dose was 12.5 mg/day (25 mg total dose over 48 hours) every 14 days (based on pre-clinical data). Dose escalation continued until the MTD was defined.

- A dose escalation phase using a 2-hour IV infusion of AZD1152 (Part B): Patients received a 2-hour IV infusion of AZD1152 repeated over 2 consecutive days every 14 days (2 days treatment followed by 12 days off treatment). The starting dose for this phase (Part B) was the total MTD from the 48-hour dosing schedule (Part A) divided into 2 equal daily infusions. If the MTD in the dose escalation phase using the 48-hour IV infusion (Part A) exceeded the MTD determined in

Study D1531C00001, the protocol allowed the MTD from Study D1531C00001 to be used in 2 equal daily doses.

For both regimens, cohorts of patients were to receive escalating doses of AZD1152 until the non-tolerated dose was reached. Dose escalation decisions were made based on cohorts of a minimum of 3 patients. The MTD was to be the dose level at which 0/6 patients or 1/6 patients had a DLT and at least 2 patients had a DLT at the next (higher) dose level; 6 evaluable patients had to be treated at the MTD.

- A safety expansion phase (Part C): Patients were to receive either the 48-hour or 2-hour AZD1152 dosing schedule, at the MTD defined for that schedule. This phase was designed to evaluate the safety, tolerability, biological activity and PK following dosing of AZD1152.

NOTE: Following an internal review of data across all 3 solid tumour studies (D1531C00001, D1531C00002 and D1531C00003), it was decided that the efficacy seen in the solid tumour patient population was not sufficient to continue these studies. AstraZeneca has temporarily suspended the development of AZD1152 in the solid tumour setting. All 3 solid tumour monotherapy studies were stopped at an appropriate stage. In the case of this study that was at the end of the dose escalation phases (Part A and Part B); no patients were enrolled in the safety expansion phase (Part C).

Eligible patients at the MTD in the dose escalation phases (Part A and Part B) and in the safety expansion phase (Part C) were also to undergo a 2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) (or FDG-PET/computed tomography [CT]) assessment[1]. This assessment was to be performed within 7 days prior to the first dose of AZD1152 (baseline), plus a further assessment after completion of Cycle 1 treatment (post-treatment), on Day 30 (±3 days) and prior to the first dose of Cycle 2. The results of the baseline FDG-PET (or FDG-PET/CT) scan were assessed to determine suitability of individual patients for follow-up scans. After discussion between investigators and AstraZeneca, patients whose tumours were clearly non-FDG-PET, did not undergo the follow-up scan. No patients were excluded from participation in the study on the basis of FDG-PET (or FDG-PET/CT) scan results.

[1] Note: The eligibility for FDG-PET (or FDG-PET/CT) assessment was expanded in Protocol Amendment 3 (10 April 2007), from only those patients in the safety expansion phase (Part C) to all patients treated at the MTD in the dose escalation phases (Part A and Part B) and in the safety expansion phase (Part C). As a result of when this amendment was introduced the majority of patients in the dose escalation phase using a 48-hour IV infusion of AZD1152 (Part A) had already discontinued the study.

Target subject population and sample size

Male or female patients aged 18 years or over. Patients were to have a solid malignancy, which was refractory to standard therapies, or for which the investigator felt no other active therapy was required for the duration of the study.

This study was expected to recruit 60 to 70 patients, recruited from 2 centres in the United States. The actual number of patients to be recruited however was dependent on the number of dose escalation steps within the study. The target number of patients with evaluable FDG-PET (or FDG-PET/CT) assessments (baseline and follow-up) was 10 per schedule (ie, 10 patients for the 48-hour schedule and 10 patients for the 2-hour AZD1152 dosing schedule). Taking into account that some tumours might not be suitable for FDG-PET (or FDG-PET/CT) assessment, it was anticipated that up to 15 patients per schedule would be recruited, in order to achieve a minimum of 10 patients with evaluable data.

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

AZD1152 was supplied to the investigator as a 100 mg lyophile together with 5 ml diluent for reconstitution of the lyophile to produce a concentrate 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. Dose escalation was to occur only based upon the toxicity information obtained at each dose level and the dose escalation decision criteria. The starting dose was 12.5 mg/day (25 mg total dose over 48 hours). Four batches of AZD1152 100 mg (Batch numbers: 32929D05, 43746A06, 41580E06 and 50757H07) and 3 batches of diluent (Batch numbers: 33317D05, 43675H06 and 41295A06) were used in this study.

Duration of treatment

AZD1152 was administered as a continuous 48-hour IV infusion or as a 2-hour IV infusion for 2 consecutive days. Patients who received the 48-hour IV infusion commenced dosing on Day 1 and Day 15 of each 28 day cycle. Patients who received the 2-hour IV infusions were dosed on Days 1, 2, 15 and 16 of each 28-day cycle. Patients could continue treatment with AZD1152 provided that the investigator considered that the patient was receiving benefit from treatment. The safety expansion phase of the study (Part C) did not go ahead.

Statistical methods

No formal statistical methods were performed on the data from this study. Data were listed and summarised. Graphical presentations of data were produced to aid interpretation.

Subject population

- A total of 37 patients were enrolled in this study and 35 patients received AZD1152. Twenty-two patients were enrolled in the dose escalation phase using a 48-hour IV infusion schedule (Part A), 2 patients did not receive treatment; 1 patient had haemoptysis and 1 patient was still responding to their previous

therapy. Fifteen patients were enrolled and received AZD1152 in the dose escalation phase using a 2-hour IV infusion schedule (Part B).

- Three of the 20 patients in the dose escalation phase using a 48-hour IV infusion schedule (Part A) had a DLT (all were in the 225 mg cohort). These were 2 DLTs of Grade 4 neutropenia (longer than 3 days) and 1 DLT of febrile neutropenia. The MTD for AZD1152 was defined as 150 mg in the dose escalation phase using a 48-hour IV infusion of AZD1152 every 14 days (Part A). Two DLTs were observed in the 300 mg cohort using the 2-hour IV infusion of AZD1152 (Part B); these were both Grade 4 neutropenia (longer than 3 days). The MTD for AZD1152 was defined as 220 mg in the dose escalation phase, using a 2-hour IV infusion of AZD1152 on 2 consecutive days every 14 days (Part B).

- Of the 35 patients treated in this study only 1 patient had not received previous chemotherapy. Twenty-seven patients had received ≥3 previous chemotherapy regimens (17 patients in the dose escalation phase using a 48-hour IV infusion [Part A] and 10 patients in the dose escalation phase using 2-hour IV infusions [Part B]). Across both dose escalation phases (Part A and Part B), 22 of the 35 patients had received previous radiotherapy (10 patients in the dose escalation phase using a 48-hour IV infusion [Part A] and 12 patients in the dose escalation phase using 2-hour IV infusions [Part B]) and 3 patients had received previous hormonal therapy (1 patient in the dose escalation phase using a 48-hour IV infusion [Part A] and 2 patients in the dose escalation phase using 2-hour IV infusions [Part B]).

- The most common tumour type in the dose escalation phase using the 48-hour IV infusion (Part A) was colon. The most common tumour types in the dose escalation phase using the 2-hour IV infusions (Part B) were lung, pleura and pancreas.

- Seven of the 35 patients who received AZD1152 in this study were identified as deviating from the protocol based on the inclusion/exclusion criteria (5 patients in the dose escalation phase using a 48-hour IV infusion [Part A] and 2 patients in the dose escalation phase using 2-hour IV infusions [Part B]). These patients were not excluded from any data summaries, listings or graphical displays and data from these patients did not affect the interpretation of the efficacy or safety data.

- All but 2 of the 35 patients discontinued the study; these patients were receiving the 2-hour IV infusion schedule (Part B) and were ongoing at data cut-off. Twenty-seven of the 35 patients discontinued due to a worsening of their condition; an additional 3 patients withdrew to a worsening of their condition and 1 patient had disease progression before they discontinued the study. One patient who received the 48-hour IV infusion schedule (Part A) died from serious adverse events (SAEs) of dehydration and hypotension; neither of these events were considered by the reporting investigator to be treatment related. One patient who received the 2-hour IV infusion schedule (Part B) discontinued treatment due an SAE of proteinuria.

Summary of efficacy results

Objective tumour response was evaluated according to Response Evaluation Criteria In Solid Tumours (RECIST).

- None of the 35 patients in this study experienced a complete response or partial response according to RECIST.
- Stable disease was reported for 8 patients (3 patients and 5 patients in the 48-hour IV infusion [Part A] and 2-hour IV infusion [Part B] schedules, respectively).
- Overall, 3 patients who received the 48-hour IV infusion (Part A) had a tumour size reduction from baseline (13%, 17% and 29%) at the first assessment (Week 8).
- Disease progression was reported for 23 patients (14 patients and 9 patients in the 48-hour IV infusion [Part A] and 2-hour IV infusion [Part B] schedules, respectively).
- No FDG-PET assessments were performed in the dose escalation phase using the 48-hour IV infusion schedule (Part A). In the dose escalation phase using a 2-hour IV schedule (Part B), no clinically meaningful changes in 2-fluoro-2-deoxy-D-glucose (FDG) uptake were observed in the 5 patients with baseline and follow-up scans (who were evaluable for both site and central review).
- Limited data were available for biomarkers on a small number of patients, which did not allow these data to be summarised or explored further.

Summary of pharmacokinetic results

Systemic exposure to AZD1152 hQPA was observed by the time of the first sample at 6 hours and 1 hour into the infusion period, for patients who received a 48-hour IV infusion (Part A) and patients that received 2-hour IV infusions (Part B), respectively. This exposure was at steady state for patients who received the 48-hour IV infusion. Exposure to AZD1152 hQPA was higher than that to AZD1152 for both regimens. The plasma concentrations of AZD1152 hQPA declined in a biphasic manner, following the end of infusion (EOI), with a terminal half-life ($t_{1/2}$) of about 10 hours and 6 hours in patients treated with a 48-hour IV infusion and 2-hour IV infusions, respectively. There was evidence of a longer third phase for both regimens, with a $t_{1/2}$ estimated to be about 50 hours and 30 hours in patients who received a 48-hour IV infusion (Part A) and 2-hour IV infusions (Part B), respectively. Low but detectable plasma levels of AZD1152 hQPA were observed in the Cycle 2 pre-dose samples. Plasma concentrations of AZD1152 declined rapidly following the EOI, being at or approaching the limit of quantification (LoQ) of the assay (0.25 ng/mL) by 4 hours post-EOI in patients who received a 48-hour IV infusion (Part A), and by 10 hours in patients who received 2-hour IV infusions (Part B). There was no evidence of accumulation of AZD1152 hQPA and exposure to AZD1152 hQPA increased in a dose proportional manner over the dose range studied.

Summary of safety results

- Review of the safety data of the 35 patients treated with AZD1152 identified no new safety concerns, other than those currently documented in the emerging safety profile for AZD1152 (ie, myelotoxicity, alopecia and stomatitis).

- The most frequently reported adverse events (AEs) for the 35 patients who received AZD1152 in the study were: fatigue (20 patients; 9 patients in the dose escalation phase using a 48-hour IV infusion [Part A], 11 patients in the dose escalation phase using 2-hour IV infusions [Part B]), nausea (14 patients; 7 patients in Part A and 7 patients in Part B) and neutropenia (13 patients; 5 patients in the dose escalation phase using a 48 hour IV infusion [Part A], 8 patients in the dose escalation phase using 2-hour IV infusions [Part B]). The majority of AEs were common terminology criteria for AEs Grade 1 or Grade 2 in toxicity.

- One patient who received the 48-hour IV infusion schedule (Part A) died due to SAEs of dehydration and hypotension; the patient died the following day. The reporting investigator did not consider either event to be related to treatment with AZD1152. The patient had advanced metastases and heavy previous treatment with chemotherapy.

- Eleven of the 35 patients had an SAE during the study (6 patients in the dose escalation phase using a 48-hour IV infusion [Part A] and 5 patients in the dose escalation phase using 2-hour IV infusions [Part B]). Febrile neutropenia was the most common SAE reported in patients receiving the 48-hour IV infusion schedule (Part A; 2 patients) and neutropenia was the most common SAE reported in patients receiving the 2-hour IV infusion schedule (Part B; 2 patients).

- Two of the 35 patients permanently discontinued treatment with AZD1152 due to an AE. One patient who received the 48-hour IV infusion schedule (Part A), discontinued treatment with AZD1152 due to SAEs of dehydration and hypotension; the patient died the following day (see above). Neither event was considered by the reporting investigator to be related to treatment. One patient who received the 2-hour IV infusion schedule (Part B), discontinued treatment with AZD1152 due to an SAE of proteinuria. This event was considered by the investigator to be related to treatment; this patient had a medical history of renal thrombosis and proteinuria at study entry.

- Principal non-clinical findings with AZD1152 were effects on the haematopoietic, lymphatic, and gastrointestinal tissues, and reversible apoptosis in the hair follicles of the skin. As a result, AEs of special interest in patients receiving AZD1152 are: myelotoxicity (particularly febrile neutropenia), stomatitis/mucositis and alopecia. There were 2 reported events of febrile neutropenia; both were in the 48-hour IV infusion schedule (Part A). Eight of the 35 patients in this study had alopecia (4 patients each in Part A and Part B) and 1 patient had stomatitis/mucositis (2-hour

IV infusion schedule [Part B]). There was no increase in the frequency of these events by dose.

- Based on the available data, no clinically relevant trends were observed in haematology or clinical chemistry parameters except for Grade 3 and Grade 4 neutropenia (Part A and Part B).

- Cardiac abnormalities were reported as expected in this patient population but no cardiac safety concerns were observed. There were no reports of patients with prolongation of the corrected QT interval with Fredericia's correction >470 ms or patients with an increase of >60 ms over baseline in this study.