AstraZeneca

Abbreviated Clinical Study Report Synopsis

Drug Substance	AZD1152
Study Code	D1531C00001
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A Phase I, Open-Label, Multi-Centre Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD1152 Given as a 2 Hour Intravenous Infusion on Two Dose Schedules in Patients With Advanced Solid Malignancies

Study dates: First patient enrolled: 23 May 2005
Last patient completed: 6 March 2008

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 at 2 centres in the Netherlands. The first patient was enrolled into this study on 23 May 2005 and the last patient completed all study procedures on 6 March 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to investigate the safety and tolerability of multiple intermittent doses of AZD1152, when given as a 2-hour infusion every 7 days and every 14 days in patients with solid malignancies, by assessment of the incidence and severity of adverse events (AEs) (common terminology criteria for adverse events [Version 3.0]), vital signs, electrocardiogram (ECG) parameters, clinical chemistry, haematology (including clotting parameters) and urinalysis.

Note: To clarify patients received AZD1152 either as a 2-hour infusion every 7 days or as a 2-hour infusion every 14 days.

The secondary objectives of this study were:

- To determine the pharmacokinetics (PK) of AZD1152 hydroxy-quinazoline pyrazole anilide (AZD1152 hQPA), and if possible AZD1152, from the observed concentration-time profiles.

- To explore the effect of AZD1152 on biomarkers of Aurora kinase activity, (including the degree of inhibition of phosphorylation of phosphohistone H3) by assessment of pharmacodynamic (PD) model parameters. The biomarkers were to include those listed in the clinical study protocol (and some others) depending on emerging data.

  Note: This objective was not met as limited data were available on a small number of patients, which did not allow for these data to be summarised or explored further.

- To explore, if the data were suitable, the relationship between plasma (AZD1152 hQPA) exposure and/or concentrations and effects on biomarkers (including the degree of inhibition of phosphorylation of phosphohistone H3). This was to be assessed using a graphical approach, appropriate modelling techniques for possible PK/PD relationships. These data were to be used along with the data from the other scheduling studies to investigate possible PK/PD relationships.

  Note: This objective was not met as limited data were available on a small number of patients, which did not allow for these data to be summarised or explored further.

- To obtain, if the data were suitable, a preliminary assessment of AZD1152 anti-tumour activity, by evaluation of tumour response using Response Evaluation Criteria In Solid Tumours (RECIST) (for patients enrolled with measurable disease) and measurement of serological biomarkers (eg, carcino embryonic antigen [CEA], prostate specific antigen [PSA]) for those patients enrolled with tumours that had serological biomarkers.

  Note: Assessment of anti-tumour activity by RECIST was performed for patients enrolled with measurable disease only. 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 for these data to be summarised or explored further.

  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:

- To investigate the effects of AZD1152 on biomarkers of tumour apoptosis and necrosis by assessment of serological biomarkers M30 and M65 and tumour biomarkers M30 and caspase 3.

  Note: Any data from analysis of AZD1152 on biomarkers of tumour apoptosis will be reported separately.

- To provide data to investigate whether any variability in the PK, safety, efficacy or PD results could possibly be explained by differences in the patient's genotype or phenotype (eg, Aurora kinase enzyme mutation):

  – Archiving paraffin embedded tumour tissue to explore the relationships between the presence of somatic mutations of candidate genes (for example those encoding Aurora kinase family members and associated pathway proteins) and response to AZD1152 will be assessed by defining the mutational status of tumours.

  – Obtaining DNA blood samples for possible future genotyping of genes that may be involved in the absorption, distribution, metabolism and excretion of AZD1152 and it's metabolites (eg, those encoding cytochrome P450 metabolising enzymes and transporter proteins) or other genes that may be involved in response to AZD1152.

  Note: Results from any genetic study may be pooled with genetic results from other studies and reported at a later date.

Study design

This was an open label, 3-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 2-hour intravenous (IV) infusion every 7 days or every 14 days 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 these schedules.

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).

- Dose escalation phase using a 7-day AZD1152 dosing schedule (Part A): In this phase, AZD1152 was administered IV over 2 hours once weekly on Days 1, 8 and 15 of a 21-day cycle. The starting dose was 100 mg. A modified accelerated titration design was used in this dose escalation phase only. Initial cohorts in this dose escalation phase consisted of 1 patient. Once the MTD was determined, an additional 6 evaluable patients were to be treated at the MTD, before moving on to the next phase of the study.

- Dose escalation phase using 14-day AZD1152 dosing schedule (Part B): In this phase, AZD1152 was administered IV over 2 hours once every 2-weeks on Day 1 and Day 15 of a 28-day cycle. Cohorts in this phase initially consisted of 3 patients and dosing started at the MTD determined in the dose escalation phase using a 7-day AZD1152 dosing schedule (Part A). Once the MTD was determined, an additional 6 evaluable patients were to be treated at the MTD, before moving on to the safety expansion phase of the study (Part C).

- Safety expansion phase (Part C): Once the MTD in the dose escalation phase using the 14-day AZD1152 dosing schedule (Part B) had been defined, further patients were planned to receive each schedule (7-day or 14-day dosing at the MTD for that schedule) to further evaluate the safety, tolerability, biological activity and PK following dosing of AZD1152, including FDG-PET assessment.

  The schedule at the MTD defined in the 14-day AZD1152 dose escalation phase (Part B) was prioritised, per the protocol. AstraZeneca considered the 14-day schedule was more suitable for the patient population studied allowing more time for recovery from events of neutropenia. Seventeen patients received the 14-day dosing schedule in the safety expansion phase (Part C).

  No patients received the 7-day schedule in the safety expansion phase (Part C). The intention was to enrol patients into 7-day schedule at the MTD following consultation with investigators regarding the issue of recovery time. However, the study was terminated due to lack of efficacy in this patient population before this was instigated.

NOTE: This study was 1 in a series of 3 studies conducted concurrently to investigate different dosing schedules for AZD1152 in advanced solid tumours. Following an internal review of data across these 3 studies, it was decided that the efficacy seen in the solid tumour patient population was not sufficient to continue. 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, the study was terminated at the end of the safety expansion phase using a 14-day schedule (Part C). AstraZeneca now believes that the best opportunity for the development of AZD1152 in patients with advanced solid malignancies may be in combination with chemotherapy.

Eligible patients at the MTD in the dose escalation phase (using the 14-day AZD1152 dosing schedule [Part B]) and in the safety expansion phase (Part C) were also to undergo a FDG-PET assessment. FDG-PET assessments were 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). The results of the baseline FDG-PET scan were assessed to determine suitability of individual patients for the follow-up scans. After discussion between investigators and AstraZeneca, patients whose tumours were clearly non-FDG-PET, did not undergo the follow-up scan. However, no patients were excluded from participation in the study on the basis of the FDG-PET scan results.

Target patient population and sample size

Male or female patients aged 18 years or over, who were likely to complete 3 weeks of treatment. 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 approximately 60 to 70 patients from up to 2 centres in the Netherlands. The actual number of patients to be recruited depended on the number of dose escalation steps in the study. For the safety expansion phase (Part C), 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 30 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 supplied either as a 10 mg/mL solution in 5 ml vials (50 mg) for preparation for IV infusion, or as a 100 mg lyophile supplied with 5 ml diluent for reconstitution to produce a 20 mg/mL concentrate for infusion. In both cases the required volume was to be further diluted in commercially available 0.9% sodium chloride injection prior to administration of AZD1152 as an IV infusion. Dose escalation was to occur based upon the toxicity information obtained at each dose level and the dose escalation decision criteria. The starting dose for the study was to be 100 mg per patient. Five batches of AZD1152 100 mg

(Batch numbers: 31241G05, 32594K05, 41580E06, 43746A06 and 50757H07) and 3 batches of diluent (Batch numbers: 43675H06, 60968F08 and 41295A06) were used in this study.

Duration of treatment

AZD1152 was administered by a 2-hour IV infusion on each dosing day. Patients in the dose escalation phase using a 7-day schedule (Part A) were dosed on Days 1, 8 and 15 of each 21-day cycle. Patients in the dose escalation phase using a 14-day schedule (Part B) were dosed on Day 1 and Day 15 of each 28-day cycle. Patients entering the safety expansion phase (Part C) received the MTD of the 14 day dosing schedule; the safety expansion phase using the 7-day administration schedule did not go ahead. 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:

- PK parameters for AZD1152 and AZD1152 hQPA were derived (where the data allowed) from the AZD1152 and AZD1152 hQPA concentration-time profiles.
- PD parameters, with particular emphasis placed on change from pre-dose levels.
- Assessment of PK/PD relationships using a graphical approach and appropriate modelling techniques.
- Evaluation of tumour response using RECIST criteria (for patients enrolled with measurable disease) and measurement of serological biomarkers (eg, CEA, PSA) (for those patients enrolled with tumours that had serological biomarkers).
- FDG-PET standard uptake value averaged over a maximum of 5 lesions, defined as those lesions with highest 2-fluoro-2-deoxy-D-glucose (FDG) uptake at baseline (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 AEs, vital signs, ECG 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. All data (including PD data) were listed and summarised. In addition (where appropriate) graphical presentations were produced to aid interpretation of these data.

Patient population

- A total of 60 patients were enrolled in this study (19 patients in the dose escalation phase using a 7-day schedule [Part A], 24 patients in the dose escalation phase using a 14-day schedule [Part B] and 17 patients in the safety expansion phase [Part C]). Fifty-nine patients received AZD1152 (1 patient who was enrolled in the safety expansion phase [Part C] did not receive treatment as they were underweight). See below for how the MTD in each dose escalation phase was determined.

- Dose escalation using a 7-day schedule (Part A) was as follows: 100 mg (1 patient, no DLTs); 200 mg (6 patients, no DLTs); 300 mg (3 patients; no DLTs); 3 of the 6 patients in the 450 mg cohort had a DLT. These were Grade 4 neutropenia (for longer than 3 days), dose delay due to neutropenia, leukopenia and thrombocytopenia of more than 7 days, and Grade 4 neutropenia and fever (reported as 2 separate AEs). An additional 3 patients were then treated at the previous dose level (300 mg) to give a total of 6 patients, per the protocol. Two DLTs were observed in the 300 mg cohort, 1 of dose delay due to neutropenia of more than 7 days and 1 of Grade 3 neutropenia for longer than 3 days. Thus, the AZD1152 450 mg and 300 mg doses were defined as non-tolerated doses and the MTD for the 7-day schedule was defined as 200 mg.

- Dose escalation using a 14-day schedule (Part B) was as follows: 200 mg (MTD of the 7-day schedule; 4 patients, no DLTs); 300 mg (3 patients, no DLTs); 450 mg (7 patients, no DLTs); 2 of the 5 patients in the 650 mg cohort had DLTs. These were febrile neutropenia and Grade 4 neutropenia for longer than 3 days. Additional patients were treated at a dose approximately midway between the last tolerated dose and the non tolerated dose per the protocol. Two patients had DLTs in the 550 mg cohort; these were febrile neutropenia and Grade 4 neutropenia for longer than 3 days. The AZD1152 650 mg and 550 mg doses were confirmed as non-tolerated doses and the MTD for the 14-day schedule was defined as 450 mg. The 450 mg dose was used in the safety expansion phase (14-day schedule).

- Of the 59 patients treated in this study, 22 patients had received ≥3 previous chemotherapy regimens (9 patients in the dose escalation phase using a 7-day schedule [Part A], 10 patients in the dose escalation phase using a 14-day schedule [Part B] and 3 patients in the safety expansion phase [Part C]). Eight patients had not received previous chemotherapy (4 patients in the dose escalation phase using a 14-day schedule [Part B] and 4 patients in the safety expansion phase [Part C]). Across the 3 phases of the study, 29 of the 59 patients had received previous radiotherapy (10 patients in the dose escalation phase using a 7-day schedule [Part A], 8 patients in the dose escalation phase using a 14-day schedule [Part B] and 11 patients in the safety expansion phase [Part C]) and 6 patients had received previous hormonal therapy (4 patients in the dose escalation phase using a 7-day schedule [Part A] and 2 patients in the safety expansion phase [Part C]).

- The most common tumour types in the dose escalation phases were colorectal (16 patients; 8 in each dose escalation phase [Part A and Part B]) and skin and soft tissue (9 patients; 3 patients and 6 patients in the dose escalation phase using a 7-day schedule [Part A] and a 14-day schedule [Part B], respectively). In the safety expansion phase (Part C), the most common tumour types were head and neck (4 patients), and skin and soft tissue (4 patients).

- Nine of the 59 patients who received AZD1152 in this study were identified as deviators, based on the inclusion/exclusion criteria in this study (1 patient who received the 7-day schedule [Part A], 2 patients who received the 14-day schedule [Part B] and 6 patients in the safety expansion phase [Part C]). These patients were not excluded from any data summaries, listings or graphical displays and did not affect the interpretation of the efficacy or safety data.

- Fifty-seven patients discontinued from the study; all 43 patients in the dose escalation phases (Part A and Part B) and 14 patients in the safety expansion phase (Part C). In total, 28 patients discontinued due to a worsening of their condition (13 patients who received the 7-day schedule [Part A], 12 patients who received the 14-day schedule [Part B] and 3 patients in the safety expansion phase [Part C]); an additional 18 patients had disease progression before discontinuing from the study. Seven patients were discontinued due to an AE; 3 patients in each of the dose escalation phases (Part A and Part B) and 1 patient in the safety expansion phase (Part C).

Summary of efficacy results

Objective tumour response was evaluated according to RECIST.

- None of the 59 patients in this study experienced a complete response (CR) or partial response (PR) according to RECIST.

- Stable disease was reported for 15 patients (7 patients and 3 patients in the dose escalation phases using a 7-day and 14-day schedule [Part A and Part B], respectively, and 5 patients in the safety expansion phase).

- Disease progression was reported for 28 patients (7 patients and 14 patients in the dose escalation phases using a 7-day and 14-day schedule [Part A and Part B], respectively, and 7 patients in the safety expansion phase [Part C]).

- There was no evidence of anti-tumour activity in any phase of the study.

- No significant changes in FDG uptake were observed in the 13 patients with baseline and follow-up scans (1 patient who received the 14-day schedule [Part B] and 12 patients in the safety expansion phase [Part C]).

- Limited data were available for biomarkers on a small number of patients, as a result biomarkers were not summarised or explored further.

Summary of pharmacokinetic results

Following a 2-hour infusion of AZD1152 systemic exposure to AZD1152 hQPA was observed by the time the first sample was taken at 1 hour into the infusion. The maximum observed plasma concentration of AZD1152 hQPA occurred at the end of the infusion (EOI), following which plasma concentrations declined in a biphasic manner with a terminal half-life ($t_{1/2}$) of about 7 hours. There was evidence of a third phase, with very low but quantifiable plasma concentrations of AZD1152 hQPA in the pre-dose sample taken before the start of the next cycle irrespective of regimen, and the $t_{1/2}$ for this third phase was estimated to be about 50 hours. There was no accumulation of AZD1152 hQPA on repeat administration for either regimen, and the majority of the AZD1152 hQPA area under plasma concentration-time curve from zero to infinity (AUC) (about 75%) was observed in the time period up to 24 hours post-infusion. Based on the maximum plasma concentration and AUC of AZD1152 hQPA the exposure to AZD1152 hQPA increased with increasing dose.

After the EOI, plasma concentrations of AZD1152 declined rapidly in a biphasic manner with a $t_{1/2}$ of between 3 to 9 hours. By 24 hours post-infusion, plasma concentrations of AZD1152 were at or approaching the limit of quantification of the assay of 0.25 ng/mL, irrespective of dose level. The exposure (assessed by AUC) to AZD1152 hQPA was higher than that to AZD1152 by 1.6-fold to 5.6-fold across the doses studied.

Summary of safety results

- Review of the safety data of the 59 patients enrolled in this study identified no safety concerns, other than those currently documented in the emerging safety profile for AZD1152 (i.e., myelotoxicity, alopecia and stomatitis).

- The most frequently reported AEs for the 59 patients in the study were: neutropenia (38 patients; 13 patients in the dose escalation phase using a 7-day schedule [Part A], 19 patients in the dose escalation phase using a 14-day schedule [Part B] and 6 patients in the safety expansion phase [Part C], nausea (27 patients; 5 patients in Part A, 14 patients in Part B and 8 patients in Part C), leukopenia (23 patients; 5 patients in Part A, 13 patients in Part B and 5 patients in Part C) and fatigue (21 patients; 6 patients in Part A, 9 patients in Part B and 6 patients in Part C). The majority of AEs were Grade 1 or Grade 2 in toxicity.

- Fourteen of the 59 patients had a serious adverse event (SAE) during the study (3 patients in the dose escalation phase using a 7-day schedule [Part A], 8 patients in the dose escalation phase using a 14-day schedule [Part B] and 3 patients in the safety expansion phase [Part C]). Abdominal pain, febrile neutropenia, neutropenia and leukopenia were the most common SAEs reported across the 3 phases of this study; 2 events of each term were reported.

- There were no deaths resulting from AEs in the study.

- Seven of the 59 patients permanently discontinued treatment with AZD1152 due to an AE (3 patients in the dose escalation phase using a 7-day schedule [Part A], 3 patients in the dose escalation phase using a 14-day schedule [Part B] and 1 patient in the safety expansion phase [Part C]). The only event to be reported for more than 1 patient was pyrexia; reported for 1 patient in each of the dose escalation phases (Part A and Part B). None of the events leading to discontinuation were considered by the reporting investigator to be related to AZD1152.

- 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 3 reported events of febrile neutropenia (2 patients in the dose escalation phase using a 14-day schedule [Part B] and 1 patient in the safety expansion phase [Part C]). Thirteen of the 59 patients had alopecia (3 patients Part A, 5 patients in Part B and 5 patients in Part C). Six patients had stomatitis/mucositis (2 patients in Part A, 1 patient in Part B and 3 patients in Part C). 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.

- 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 greater than 470 ms or patients with an increase of greater than 60 ms over baseline in this study.