AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7762
Study Code	D1040C00002
Date	18 January 2011

A Phase I, Open-Label, Multi-Center, Dose-Escalation Study to Assess Safety, Tolerability, and Pharmacokinetics of AZD7762 Administered as a Single Intravenous Agent and in Combination with Weekly Standard Dose Gemcitabine in Patients with Advanced Solid Malignancies

Study dates: First subject enrolled: 14 December 2006
Last subject last visit: 06 May 2010

Phase of development: Clinical pharmacology (I)

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

Study center

The study was conducted at 3 centers in the United States. All centers were initiated, received study drug, and admitted patients.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary objective of this study was to assess safety and tolerability of AZD7762 alone and in combination with gemcitabine, by assessment of Common Terminology Criteria Adverse Events version 3.0 (CTCAE) grade and type of adverse events (AEs), changes in laboratory values, vital signs, cardiac markers, and left ventricular ejection fraction (LVEF).

The secondary objectives of this study were:

- To determine the single-dose PK of AZD7762 when administered alone by assessment of C_{max}, area under the plasma concentration-time curve from zero to infinity (AUC), area under the plasma concentration-time curve to the last quantifiable plasma concentration ($AUC_{(0-t)}$), clearance (CL), half-life associated with terminal slope of a semi-logarithmic concentration-time curve ($t_{½\lambda z}$), mean residence time (MRT), volume of distribution at steady state (Vss), plasma drug concentration at 24 hours after administration of a given dose (C_{24h}), cumulative amount of unchanged drug excreted into urine (A_e), renal clearance of drug from plasma (CL_r), and area under plasma concentration-time curve from zero to 48 hours ($AUC_{(0-48h)}$).

- To compare the clearance (CL) of AZD7762 and gemcitabine when given as a single agent to the corresponding CL value when AZD7762 and gemcitabine are given in combination.

- To seek preliminary evidence of the anti-tumor activity of AZD7762 administered in combination with gemcitabine by assessment of Response Evaluation Criteria in Solid Tumors (RECIST version 1.0).

- To assess the effects of gemcitabine alone and in combination with AZD7762 on a relevant pharmacological biomarker (phosphorylated checkpoint kinase 1 [pChk1]) and a biomarker for DNA repair and apoptosis (pH2AX) in surrogate tissue (skin with hair follicles) and tumor biopsies.

- To select dose(s) for further evaluation in Phase II studies.

The exploratory objectives of this study were:

- To explore the relationship between the dose or PK of AZD7762 and changes in biomarkers (pChk1 and pH2AX) in surrogate tissue (skin with hair follicles) and

tumor biopsies by assessment of dose, C_{max}, AUC, and C_{24h} and changes in biomarkers.

- To investigate metabolites of AZD7762 in plasma or urine.
- To explore the relationship between p53 and MDM2 tumor expression (and other genes/proteins implicated in the cell cycle) and clinical response.
- Optional: In consenting patients, to obtain a blood sample for DNA extraction for retrospective pharmacogenetic analysis.

Study design

This was an open-label, multi-center, dose-escalation, Phase I study to evaluate safety, tolerability, pharmacokinetics, and tumor response, and to investigate biomarker changes of AZD7762 alone and in combination with gemcitabine.

The starting dose of AZD7762 was 6 mg administered IV. The original design was based on a 4 week treatment schedule for the first 7 patients enrolled at the AZD7762 6 mg dose level. The remaining patients were enrolled into the study based on a 3 week treatment schedule. The dose escalation of AZD7762 was to occur based on the required safety, tolerability, and PK information obtained from a minimum of 3 evaluable patients during Cycles 0 and 1. The percent increase was at the discretion of the investigators and AstraZeneca based on emerging safety data from this study and from a corresponding study of AZD7762 in combination with irinotecan (D1040C00004).

In Cycle 0, patients received single dose AZD7762 administered as a 60 minute IV infusion on Days 1 and 8 followed by a rest week. Following the completion of Cycle 0, AZD7762 was administered on Days 1 and 8 in combination with gemcitabine followed by a rest week. Dose escalation (3+3) decisions were based on the required safety, tolerability and PK information obtained from a minimum of 3 evaluable patients during Cycle 0 and Cycle 1.

Target subject population and sample size

Approximately 60 patients with advanced solid malignancies were planned dosed with AZD7762, depending on the number of dose escalations, replacement patients, or expansions required. Investigators were encouraged to enroll patients with advanced solid malignancies for whom single-agent weekly gemcitabine therapy as described in the protocol was considered appropriate.

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

AZD7762 was manufactured by AstraZeneca and supplied as either 5 or 7 mL of aqueous solution at 6 mg/mL in single-dose vials. Five batches of AZD7762 were used in this study. Individual batch numbers are included in the Clinical Study Report. Gemcitabine was commercially available and was not supplied by AstraZeneca.

Duration of treatment

Once a dose level was completed, the patients on that dose level who were, in the Investigator's opinion, continuing to benefit and had not experienced cardiac dose-limiting toxicity (or any other untolerable toxicity) during Cycle 1, could continue on the study medication administered in combination with gemcitabine until protocol completion. Patients could receive treatment in 3 week cycles as long as they were benefiting from treatment, there was no evidence of disease progression, they met no other withdrawal criteria, and they continued to receive gemcitabine therapy.

Statistical methods

There were no formal inferential statistical analyses comparing dose groups in this study. All safety, tolerability, PD, PK, and initial indication of efficacy data were summarized using descriptive statistics and exploratory graphical presentations of the data. Descriptive statistics for continuous data includes N, arithmetic mean, standard deviation (SD), minimum, median, and maximum, unless otherwise specified. Categorical data summaries include N, count, and % in each category, by dose, as well as N, count, and % across all doses combined.

Subject population

A total of 64 patients were enrolled into the study at 3 study sites; 42 of these patients received at least 1 dose of AZD7762. The mean age of the patients in the safety analysis set was 58.2 years (range 29 to 72). The majority of patients were Caucasian (30 patients, 71.4%) and 18 to 64 years of age (32 patients, 76.2%). The number of males and females in the study were roughly equal (22 males, 52.4%; 20 females, 47.6%).

Slightly more than half of the patients (23 patients, 54.8%) in the safety analysis set had an ECOG Performance Status indicating restricted activity level. A majority of the patients (31 patients, 73.8%) had 1 to 2 local/metastatic sites. The time from initial diagnosis to enrollment in the study was greater than 12 months for most of the patients, either >12 to ≤36 months for 16 patients (38.1%) or greater than 36 months for 17 patients (40.5%). The time from last diagnosis to enrollment in the study was less than or equal to 3 months for 32 patients (76.2%). There was a broad representation of primary tumor types in the study population, with colorectal (colon + colorectal combined) and lung being the most common.

Four of the 42 patients in the Safety analysis set were not eligible for DLT analysis: 2 patients due to incorrect enrollment and 2 patients due to disease progression before the evaluable period.

Summary of pharmacokinetic results

The mean plasma concentration-time profiles of AZD7762 alone and AZD7762 in combination with gemcitabine appeared to be similar for all dose levels. Though the number of patients per dose level was limited (from 3 to 6 patients per dose level), AZD7762 exposure in terms of AUC, C_{max}, and C_{24h} appeared to increase with increasing dose in a roughly linear and proportional manner. The average $t_{½}$ across all dose levels ranged from 7.95 hours to

15.5 hours for AZD7762 alone and between 6.29 hours and 18.1 hours for AZD7762 in combination with gemcitabine.

Overall, administration of gemcitabine with AZD7762 did not appear to change the CL of AZD7762. For AZD7762 administered alone, gmean CL ranged from 35.0 to 72.9 L/h. A statistical analysis to compare the clearance of AZD7762 administered alone versus AZD7762 administered with gemcitabine showed no difference. The estimated % difference in clearance (AZD7762 + gemcitabine-AZD7762 alone) was -6.1 (CI -18.9-8.8, p=0.4750).

Urine samples were collected only during treatment with AZD7762 alone and the analysis of urine PK parameters indicate that on average 11.1% to 19.9% of unchanged drug is excreted in urine across all dose levels.

Summary of pharmacodynamic results-Effects of gemcitabine alone and in combination with AZD7762 on pChk1 and pH2AX in surrogate tissue and tumor biopsies

No paired tumor biopsies were available from this study; therefore, the effect of gemcitabine alone and in combination with AZD7762 with could only be evaluated on surrogate tissue. The amount of % staining for both biomarkers was minimal (<25%) and as a result, the H-scores for both biomarkers took 2 values (0 or 3). Summaries of staining results therefore concentrated on the degree of % staining. No dose response was observed for percent staining following AZD7762 treatment. No increase in percent staining of pChk1 and pH2AX was seen at AZD7762 doses less than 32 mg. While there were small increases in staining for the patients in the 32 mg cohort (the NTD), this result was not confirmed by increased staining in the 40 mg cohort.

Dose and/or concentration response relationships- Relationship between the dose or PK of AZD7762 and changes in pChk1 and pH2AX in surrogate tissue and tumor biopsies

Due to the small number of patients in this study and the limited staining observed in the surrogate (skin) biopsies (staining was observed at 32 mg AZD7762 only), pharmacokinetic/pharmacodynamic modeling was not performed.

Summary of efficacy results

A partial response was observed in 2 patients, 1 at 6 mg AZD7762 + 750 mg/m^2 gemcitabine and 1 at 9 mg AZD7762 + 1000 mg/m^2 gemcitabine. Both patients had lung adenocarcinoma (non-small cell lung cancer, NSCLC) as the primary tumor location and type. Neither patient had previously been treated with gemcitabine. Seven patients had a best response of "not evaluable" due to the lack of an evaluable post-baseline scan. For the remaining patients, the best overall response was stable disease or disease progression.

Summary of safety results

The median duration of exposure to AZD7762 across all doses of was 43 days (range: 1 to 318 days), with the longest median duration in the 9 mg dose cohort. The median number of cycles completed was 3 (range: 0 to 13 cycles). The overall AZD7762 mean dose intensity

was greater than 90% for all cycles. Dose intensity was 92.1%, 91.0% and 96.3% for Cycles 1, 2, and 3, respectively.

The MTD for this study was determined to be 30 mg AZD7762 in combination with gemcitabine. Cardiac DLTs were reported in 2 patients during Cycle 0 when AZD7762 was administered alone without chemotherapy. A Common Terminology Criteria for Adverse Events (CTCAE; Version 3.0) Grade 3 elevated troponin I with no concomitant clinical or echocardiograph/ECG changes was recorded for 1 patient at the 32 mg AZD7762 dose. The event was reversible following discontinuation of AZD7762. A CTCAE Grade 3 myocardial ischemia associated with chest pain, ECG changes, decreased EF, and elevated troponin I as high as 0.25 (Grade 3) was recorded for 1 patient at the 40 mg AZD7763 dose. Study treatment was discontinued and all events were reversible following discontinuation of AZD7762. Non-cardiac DLTs occurred in 2 patients during Cycle 1: CTCAE Grade 3 nausea and vomiting in 1 patient at 32 mg AZD7762, and CTCAE Grade 4 neutropenia in 1 patient at 40 mg AZD7762.

Nearly all patients (95.2%) experienced an AE in the study. The most commonly reported AEs in the study were fatigue (40.5%) and nausea, neutropenia, and pyrexia (26.2% each). During Cycle 0 (AZD7762 alone), 59.5% of patients experienced an AE and the most frequently reported AEs were fatigue, vomiting (14.3% each), and nausea (11.9%).

Table S1 presents the CTCAE ≥Grade 3 adverse events by preferred terms from the Medical Dictionary for Regulatory Affairs (MedDRA; Version 13.0) for the 26 patients (61.9%) who reported these events. The most commonly reported of these AEs was neutropenia (16.7%). During Cycle 0, 16.7% of patients experienced an AE of CTCAE Grade 3 or higher and from Cycle 1 onwards, 52.4% of patients experienced an AE of CTCAE Grade 3 or higher.

Less than half of the patients in the study (42.9%) experienced an AE that was causally related to AZD7762. The most frequently reported of these causally related AEs were neutropenia (14.3%) and fatigue (11.9%). It should be noted that there were no reports of neutropenia, decreased platelet count, or hypophosphatemia during Cycle 0 when AZD7762 was administered alone (without chemotherapy).

A total of 7 deaths occurred during the study: 1 due to an SAE (endocarditis) and 6 due to disease progression. The endocarditis was not considered by the investigator to be causally related to AZD7762 or gemcitabine. SAEs occurred in patients at all AZD7762 doses except the 9 mg dose. Twelve patients (28.6%) experienced SAEs (including the event with the outcome of death); 3 patients (7.1%) experienced SAEs that were considered causally related to AZD7762, and 4 patients (9.5%) experienced SAEs that were considered causally related to gemcitabine. Two patients (4.8%) had an AE leading to discontinuation (DAE); one patient (2.4%) had a DAE that was considered causally related to AZD7762. No patient had a DAE that was considered causally related to gemcitabine.

A total of 32 patients had laboratory values of CTCAE Grade 3 or 4; the most frequently recorded event was total ANC reductions (14 patients). Other frequently recorded events were reductions in leucocytes and platelets and increases in activated partial thromboplastin

time. Changes in non-hematological laboratory parameters included increases in transaminases (particularly at AZD7762 doses >32 mg). Mild increases in non-fasting glucose levels and decreases in serum phosphate levels were also recorded and were not dose-dependent. No clinically relevant, treatment-emergent changes in urinalysis parameters were observed.

There were no clinically relevant, treatment-emergent changes or trends in blood pressure or heart rate for patients following exposure to AZD7762. There were no clinically important changes in physical findings or other observations related to safety in this study.

Table S1 **Number (%) of patients who had at least 1 adverse event of CTCAE Grade 3 or higher (reported by ≥2 patients) by system organ class and preferred term (Safety analysis set)**

		AZD7762 dose (mg)/gemcitabine dose (mg/m^2)								
System organ class Preferred term[a]	**Total n=42**	**6/750**[b] **(n=6)**	**6/1000**[b] **(n=1)**	**6/1000 (n=2)**	**9/1000 (n=3)**	**14/1000 (n=6)**	**21/1000 (n=3)**	**30/1000 (n=7)**	**32/1000 (n=6)**	**40/1000 (n=8)**
Patients with any AE of CTCAE Grade ≥3	**26 (61.9)**	**6 (100.0)**	**1 (100.0)**	**1 (50.0)**	**1 (33.3)**	**2 (33.3)**	**1 (33.3)**	**4 (57.1)**	**4 (66.7)**	**6 (75.0)**
Blood and lymphatic system disorders	11 (26.2)	2 (33.3)	1 (100.0)	0	1 (33.3)	1 (16.7)	1 (33.3)	1 (14.3)	1 (16.7)	3 (37.5)
Neutropenia	7 (16.7)	0	1 (100.0)	0	0	1 (16.7)	0	1 (14.3)	1 (16.7)	3 (37.5)
Anemia	2 (4.8)	2 (33.3)	0	0	0	0	0	0	0	0
Thrombocytopenia	2 (4.8)	0	0	0	1 (33.3)	0	0	0	0	1 (12.5)
Metabolism and nutrition disorders	8 (19.0)	2 (33.3)	0	0	0	0	0	3 (42.9)	1 (16.7)	2 (25.0)
Hyperglycemia	3 (7.1)	0	0	0	0	0	0	1 (14.3)	0	2 (25.0)
Hyponatremia	2 (4.8)	1 (16.7)	0	0	0	0	0	0	1 (16.7)	0
Hypophosphatemia	2 (4.8)	0	0	0	0	0	0	2 (28.6)	0	0

[a] A patient can have one or more preferred term (PT) reported under a given SOC. A patient is only counted once for each PT.
[b] Patients in these dose groups were treated 3 times a cycle (3 out of 4 weeks). Following Amendment 3, patients were treated 2 times a cycle (2 out of 3 weeks).
MedDRA Medical dictionary for regulatory activities (version 13.0); AE Adverse event.