AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7762
Study Code	D1040C00008
Edition Number	1
Date	15 November 2011

A Phase I, Open-Label, 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 Japanese Patients with Advanced Solid Malignancies

Study dates: First subject enrolled: 7 June 2009
Last subject last visit: 25 February 2011

Phase of development: Clinical pharmacology (I)

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess safety and tolerability of AZD7762 alone and in combination with gemcitabine.	Common Terminology Criteria Adverse Events version 3.0 (CTCAE) grade and type of adverse events (AEs), changes in laboratory values, vital signs, cardiac markers, ECG and left ventricular ejection fraction (LVEF).	Safety
Secondary	**Secondary**	
To determine the single-dose PK of AZD7762 when administered alone.	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 (V_{ss}), and plasma drug concentration at 24 hours after administration of a given dose (C_{24h})	PK
To compare the CL of AZD7762 when given as a single agent to the corresponding CL value when AZD7762 and gemcitabine are given in combination	CL of AZD7762 single dose, CL of AZD7762 in combination with gemcitabine	PK
To seek preliminary evidence of the anti-tumour activity of AZD7762 administered in combination with gemcitabine	Objective tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST)	Efficacy
Exploratory*	**Exploratory**	
To explore the relationship between p53 and MDM2 tumor expression (and other genes/proteins implicated in the cell cycle) and clinical response	p53 and MDM2 tumor expression (and other genes/proteins implicated in the cell cycle) and clinical response	PD
Optional: In consenting patients, to obtain a blood sample for DNA extraction for retrospective pharmacogenetic analysis	Collection of a blood sample for DNA extraction and storage.	Pharmaco-genetics

DNA: Deoxyribonucleic acid
MDM2: A gene involved in the regulation of p53
p53: Tumour suppressor protein p53
* Exploratory objectives results are not reported in the CSR synopsis.

Study design

This was an open-label, dose-escalation, Phase I study to evaluate the safety, tolerability, pharmacokinetics and tumor response when AZD7762 was administered alone and in combination with gemcitabine.

Target subject population and sample size

Japanese patients with advanced solid malignancies for whom single agent weekly standard dose of gemcitabine therapy was considered appropriate.

Approximately 30 patients with advanced solid malignancies were enrolled in this study, depending on the number of dose escalations required. A minimum of three and up to six evaluable patients were to be enrolled in each dose level.

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

Gemcitabine was administered as a 30-minute IV infusion. AZD7762 was administered as a 60-minute intravenous (IV) infusion immediately upon completion of gemcitabine infusion. The starting dose of AZD7762 was 6 mg. A dose of AZD7762 in the next patient cohort was selected based on the available safety and PK data from all evaluable patients in this study and the overseas study (Study code: D1040C00002). The dose of gemcitabine was a full standard dose of 1000 mg/m^2 and was adjusted according to label and standard local practice.

Patients received a single dose of AZD7762 2 doses at a one week interval (Cycle 0). After the confirmation of patients' safety during Cycle 0, patients received AZD7762 in combination with gemcitabine 2 doses at a one week interval followed by a rest week (1 cycle=3 weeks). Dose escalation was to proceed until any of the defined stopping criteria for dose escalation had been met.

Duration of treatment

Following the completion of Cycles 0 and 1, individual patients continued treatment indefinitely after giving consent to the continued study treatment, provided that in the opinion of the Investigator: (a) they were continuing to benefit, (b) there was no evidence of disease progression, and (c) they did not meet any other withdrawal criteria.

Statistical methods

All safety, tolerability and PK data were summarized using descriptive statistics and exploratory graphical presentations of the data. All summaries were presented by dose and cycle.

Subject population

A total of 24 patients were enrolled into the study, and 20 patients received at least 1 dose of AZD7762 (3 patients in 6 mg cohort, 3 patients in 9 mg cohort, 6 patients in 21 mg cohort, and 8 patients in 30 mg cohort, safety analysis set). Seventeen patients were eligible for DLT

evaluation in the dose escalation and safety expansion phases. The reason for ineligibility for DLT evaluation in the 3 patients (1 patient in 21 mg cohort, and 2 patients in 30 mg cohort) was not completing Cycles 0 and 1 of treatment.

The mean age of the patients in the safety analysis set was 60 years (range 47 to 72). Fourteen patients (70%) were male and 8 (40%) patients were WHO performance status 0. Primary tumour was lung in 14 patients (70%), rectal in 3 patients (15%), and pleura, colon and colorectal in each one patient (5%). A majority of the patients (18 patients, 90%) had at least one metastatic site. All patients received at least one previous chemotherapy.

All patients discontinued the study treatment by the data cut-off for this report. A total of 13 patients discontinued the study treatment due to disease progression, 6 patients due to AE(s), and 1 patient due to the study termination decision.

Summary of pharmacokinetic results

- The disposition of AZD7762 following a single dose constant IV infusion may be described as multi-phasic with an initial rapid decline (distribution phase) followed by a slower decline (elimination phase).
- The maximum plasma concentration (C_{max}) was achieved at end of infusion at approximately 1 hour from start of infusion (T_{max}).
- AZD7762 was extensively distributed with an average steady-state volume of distribution (V_{ss}) range of 382 L to 601 L across all dose levels after single dose administration.
- AZD7762 was systemically cleared with an average elimination half-life range of 16.1 hours to 19.4 hours across all dose levels after single dose administration. In combination with gemcitabine, the average $t_{1/2}$ across all dose levels ranged between 15.6 hours and 18.3 hours.
- AZD7762 systemic exposure as described by C_{max} and AUC appear to increase in a roughly linear manner with dose over the dose range studied (6 mg to 30 mg).
- Between subject variability in PK parameters were low to moderate (10 - 45% CV).
- Gemcitabine did not affect the pharmacokinetics of AZD7762 when given in combination.
- Overall, administration of gemcitabine with AZD7762 did not appear to change the CL of AZD7762.
- The gmean CL ranged from 22.0 to 32.7 L/h for AZD7762 administered alone, and ranged from 21.1 to 24.4 L/h in combination with gemcitabine.

Summary of efficacy results

Neither complete response nor partial response was reported in the study. Stable disease (SD) was observed in 5 patients with lung cancer (1 patient in 9 mg cohort, 2 patients in 21 mg cohort, and 2 patients in 30 mg cohort). The minimum period of SD was defined as 8 weeks in this study.

Summary of safety results

The median duration of exposure to AZD7762 was 47 days in 6 mg cohort, 65 days in 9 mg cohort, 26 days in 21 mg cohort, and 45 days in 30 mg cohort. The median duration of cycles completed was 3 cycles in 6 mg cohort, 4 cycles in 9 mg cohort, 2 cycles in 21 mg cohort, and 3 cycles in 30 mg cohort with a longest treatment period (176 days) reported in one patient with lung cancer in 30 mg cohort. The AZD7762 mean dose intensity for the first 3 cycles was greater than 90% in each cohort.

The MTD for this study was determined to be 21 mg AZD7762 in combination with gemcitabine 1000 mg/m^2 based on 5 evaluable patients safety information, as the study had to be terminated early. There was no DLT in 5 patients in 21 mg cohort.

DLT was identified in two patients in 30 mg in combination with gemcitabine 1000 mg/m^2. One cardiac DLT (troponin T increased on CTCAE grade 3) was recorded in 1 patient when AZD7762 was administered alone (Day 1 in Cycle 0). Liver function and haematological related DLT (ALT increased, AST increased, neutropenia and thrombocytopenia) were recorded in the other patient in the combination period (Day 15 in Cycle 1; one week after the second administration of AZD7762 in combination with gemcitabine). Study treatment was discontinued and all events were reversible following discontinuation of AZD7762 (and gemcitabine). Therefore 30 mg was regarded as non-tolerable dose in this study.

Nearly all patients (19 of 20 patient, 95%) experienced an AE in this study. The most commonly reported AEs in the study were bradycardia (11/20 patients, 55%), neutropenia (9/20 patients, 45%), fatigue (6/20 patients, 30%), hypertension (6/20 patients, 30%), and rash (6/20 patients, 30%). These AEs were mild or moderate except for neutropenia. During Cycle 0, 90% of patients experienced an AE and the most frequently reported AEs were bradycardia (10/20 pts), hypertension (5/20 pts) and fatigue (3/20 pts).

A total of 11 patients (55%) reported CTCAE grade ≥3 AEs (Table S2). The most commonly reported AEs with CTCAE grade 3 or higher were neutropenia (9/20 pts), leucopenia (5/20 pts), ALT increased and AST increased (2/20 pts, respectively). One event (Troponin T increased) in 1 patient was reported as a CTCAE grade ≥3 AE during Cycle 0.

No patient died due to an AE. Serious AE (SAE) were reported for 5 patients (25.0%). A drug related SAE judged by the investigators was reported in 2 patients (Table S3).

Six patients discontinued the study treatment due to an AE (2/6 patient also had a SAE).

A total of 12 patients (24 laboratory items) had laboratory values of CTCAE grade 3 or 4 (as the worst grade during treatment period). The most frequently recorded event was total absolute neutrophil count (9 patients). Other frequent recorded events were reductions in leucocytes (5 patients).

Table S2 Number (%) of patients who had at least 1 AE of CTCAE grade 3 or higher by system organ class and preferred term (Safety analysis set)

System Organ Class	AZD7762 dose (mg) / gemcitabine dose (mg/m^2)				
Preferred Term[a]	**6/1000 (n=3)**	**9/1000 (n=3)**	**21/1000 (n=6)**	**30/1000 (n=8)**	**Total (n=20)**
Patients with Any AE of CTCAE grade >= 3	**2 (66.7)**	**1 (33.3)**	**3 (50.0)**	**5 (62.5)**	**11 (55.0)**
Blood and lymphatic system disorders	2 (66.7)	1 (33.3)	3 (50.0)	4 (50.0)	10 (50.0)
Neutropenia	2 (66.7)	1 (33.3)	2 (33.3)	4 (50.0)	9 (45.0)
Leukopenia	2 (66.7)	0	1 (16.7)	2 (25.0)	5 (25.0)
Febrile neutropenia	1 (33.3)	0	0	0	1 (5.0)
Thrombocytopenia	0	0	0	1 (12.5)	1 (5.0)
Investigations	0	0	2 (33.3)	2 (25.0)	4 (20.0)
Alanine aminotransferase increased	0	0	1 (16.7)	1 (12.5)	2 (10.0)
Aspartate aminotransferase increased	0	0	1 (16.7)	1 (12.5)	2 (10.0)
Blood sodium decreased	0	0	1 (16.7)	0	1 (5.0)
Haemoglobin decreased	0	0	1 (16.7)	0	1 (5.0)
Troponin T increased	0	0	0	1(12.5)	1 (5.0)
Gastrointestinal disorders	0	1 (33.3)	0	0	1 (5.0)
Diarrhoea	0	1 (33.3)	0	0	1 (5.0)
Infection and infestations	0	1 (33.3)	0	0	1 (5.0)
Bacteraemia	0	1 (33.3)	0	0	1 (5.0)
Metabolism and nutrition disorders	0	0	0	1 (12.5)	1 (5.0)
Hypophosphataemia	0	0	0	1 (12.5)	1 (5.0)

a A patient can have one or more PT reported under a given SOC. A patient is only counted once for each PT
MedDRA version 13.1

Table S3 Listing of key information for SAEs (Safety analysis set)

Starting dose (AZD7762 /gemcitabine)	Patient No.	Age (years)	Sex	Episode term as reported by investigator	MedDRA Preferred Term Name	Maximum CTCAE Grade	Time from start of treatment to onset of AE (days)	Time from last dose to onset of AE (days)	Time from onset of AE to becoming serious (days)	Reasonable possibility AE caused by AZD7762
6 mg/ 1000 mg/m^2	E0001002	52	Male	Febrile neutropenia	Febrile neutropenia	3	50	28	50	No
9 mg/ 1000 mg/m^2	E0001004	69	Male	Bacteremia	Bacteraemia	3	93	22	96	No
	E0001005	72	Male	Drug-induced interstitial pneumonea	Interstitial lung disease	2	78	14	78	Yes
21 mg/ 1000 mg/m^2	E0001007	65	Male	Bronchitis	Bronchitis	2	56	-57	56	No
30 mg/ 1000 mg/m^2	E0001017	50	Male	Alanine Aminotransferase increased	Alanine aminotransferase increased	3	21	-1	29	Yes
				Aspartate Aminotransferase increased	Aspartate aminotransferase increased	3	21	-1	29	Yes
				Leukocytopenia	Leukopenia	4	21	-1	29	Yes
				Neutropenia	Neutropenia	4	21	-1	29	Yes
				Gamma -GTP increased	Gamma-glutamyltransferase increased	2	29	8	29	Yes
				Thrombocytopenia	Thrombocytopenia	4	29	8	29	Yes

MedDRA version 13.1