Clinical Study Report Synopsis

Drug Substance	AZD7762
Study Code	D1040C00004
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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 Irinotecan in Patients with Advanced Solid Malignancies

Study dates:	First subject enrolled: 10 May 2007 Last subject last visit: 21 January 2010
Phase of development:	Clinical pharmacology (I)
International Co-ordinating Investigator:	
Sponsor's Responsible Medical Officer:	

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 irinotecan, 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 irinotecan when given as a single agent to the corresponding CL value when AZD7762 and irinotecan are given in combination.

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

- 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 irinotecan.

The starting dose of AZD7762 was 6 mg administered IV. The original design was based on a 4-week treatment schedule for the first 5 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.

In Cycle 0, patients received single dose AZD7762 monotherapy 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 irinotecan 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 50 patients with advanced solid malignancies were planned to be 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 irinotecan 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. Eight batches of AZD7762 were used in this study. Individual batch numbers are included in Clinical Study Report Appendix 12.1.6. Irinotecan 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 0 or Cycle 1, could continue on the study medication administered in combination with irinotecan 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 irinotecan 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 96 patients were enrolled into the study at 3 study sites; 28 patients failed screening and 68 patients received at least 1 dose of AZD7762 (safety analysis set). Fifty-seven patients were eligible for DLT evaluation in the dose escalation and safety expansion phases. The most common reason for ineligibility for DLT evaluation was not completing Cycles 0 and 1 of treatment.

The mean age of the patients in the safety analysis set was 56.3 years (range 33 to 74). The majority of patients were Caucasian (60 patients, 88.2%) and 18 to 64 years of age (54 patients, 79.4%). The number of males and females in the study were roughly equal (35 males, 51.5%; 33 females, 48.5%). A total of 26 patients (38.2%) in the safety analysis set had an ECOG Performance Status indicating restricted activity level. A majority of the patients (41 patients, 60.3%) had 3 to 6 local/metastatic sites. The time from initial diagnosis to enrollment in the study was >12 to ≤36 months for 32 patients (47.1%), greater than 36 months for 27 patients (39.7%), and >6 months to ≤12 months for 8 patients (11.8%). The time from last diagnosis to enrollment in the study was less than or equal to 3 months for 60 patients (88.2%). There was a broad representation of primary tumor types in the study population, with colon/colorectal/rectal/ anal/anorectum/duodenum combined (34 patients total) being the most common.

Summary of pharmacokinetic results

The disposition of AZD7762 can be described as multi-exponential with a rapid distribution phase followed by a slower elimination phase. The mean plasma concentration-time profiles of AZD7762 alone and AZD7762 in combination with irinotecan appeared to be similar for all dose levels. AZD7762 exposure in terms of AUC, C_{max}, and C_{24h} appeared to increase with increasing dose in a roughly linear manner. The average $t_{½}$ across all dose levels ranged from 5.28 hours to 13.9 hours for AZD7762 alone and between 11.0 hours and 14.1 hours for AZD7762 in combination with irinotecan. A statistically significant difference was detected in the clearance of AZD7762 administered alone compared to AZD7762 administered with irinotecan. For AZD7762 administered alone, the GLS mean estimate for CL was 37.6 L/h (90% CI: 34.5, 41.1); for AZD7762 administered with irinotecan, the GLS mean estimate for CL was 32.8 L/h (90% CI: 30.0, 35.8). The % treatment difference was 14.7 (90% CI: 8.5, 21.2) and $p<0.001$. However, it is unlikely that this difference is clinically significant and the reason for this difference is unclear. Urine samples were collected only during treatment with AZD7762 alone and the analysis of urine PK parameters indicate that on average 7.5% to 21.9% of unchanged drug was excreted in urine across all dose levels. AZD7762 metabolites could not be analyzed because plasma and urine samples were considered nonviable as a result of prolonged storage well beyond the established assay stability range.

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

Data collected were from surrogate skin biopsies only. Across all doses, percent of cells stained for Chk1 and pH2AX was low (< 5.1% for pChk1 and < 1.7% for pH2AX).

The only dose level to show consistent increased staining in both pChk1 and pH2AX following administration of AZD7762 with irinotecan compared with irinotecan alone was the 96 mg group, where 4/5 patients with evaluable data at both time points showing an increase in staining for both markers.

Summary of efficacy results

Response was determined according to RECIST (response evaluation criteria in solid tumors). A complete response (CR) was observed in 1 patient (48 mg AZD7762 + 100 mg/m^2 irinotecan; previously treated with cisplatin and etoposide) with small cell carcinoma of the ureter (duration of response 18+ months). A partial response (PR) was observed in 1 patient (144 mg AZD7762 +100 mg/m^2 irinotecan; previously treated with Avastin, irinotecan, fluorouracil, and GDC-0449) with colon cancer (duration of approximately 8 months).

Summary of safety results

The median duration of exposure to AZD7762 across all doses was 43 days (range: 1 to 541 days), with the longest median duration (86 days) in the 6 mg AZD7762 + 125 mg/m^2 irinotecan dose cohort. The median number of cycles completed was 3 (range: 0 to 26 cycles). The overall AZD7762 mean dose intensity for the first 3 cycles was 100%.

During the dose escalation phase of the study, the maximum tolerated dose (MTD) for AZD7762 was identified as 96 mg; cardiac DLTs occurred in 1 patient at 144 mg (left ventricular dysfunction, troponin I increased, and myocardial infarction; all CTCAE Grade 4) without any further DLT at 96 mg. During the safety expansion phase, 3 of 11 evaluable patients at the 96 mg dose experienced cardiac DLTs: CTCAE Grade 4 troponin increased and CTCAE Grade 2 left ventricular dysfunction (1 patient); CTCAE Grade 3 troponin I increased (1 patient); CTCAE Grade 3 cardiomyopathy (1 patient). All cardiac toxicities occurred during Cycle 0 (AZD7762 alone).

All patients had at least 1 AE. The most common AEs were diarrhea (60.3%), fatigue (50.0%), nausea (42.6%), and vomiting (27.9%). Adverse events of CTCAE Grade 3 or higher were reported for 29 patients (42.6%) in the study. The most commonly reported of these AEs were diarrhea (10.3%) and neutropenia (7.4%). Approximately half of the patients in the study (52.9%) experienced an AE that was causally related to AZD7762. The most frequently reported of the causally related AEs were fatigue (19.1%), diarrhea (17.6%), and nausea (14.7%). There were 5 deaths; all were due to disease progression. SAEs were reported for 15 patients (22.1%). The most common SAEs were diarrhea and troponin increased (4.4% each), and left ventricular dysfunction and febrile neutropenia (2.9% each). Seven patients (10.3%) had an AE leading to discontinuation (DAE); the most frequently reported DAEs were troponin increased (5.9%), and left ventricular dysfunction (2.9%).