AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2461
Study Code	D3660C00001
Edition Number	1
Date	21 September 2011

An Open-Label, Dose-Escalation Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of the PARP Inhibitor, AZD2461, in Patients with Refractory Solid Tumors

Study dates: First patient enrolled: 23 November 2010
Last patient last visit: 01 June 2011

Phase of development: Clinical Pharmacology (I)

Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

Contract Research Organization:

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

Introduction

This study is being submitted as an abbreviated clinical study report (CSR) because the study was stopped early due to the Sponsor suspending development of AZD2461, and therefore only limited data is available. The decision to stop the study was not due to any clinical safety reason.

Study centre(s)

Publications

There were no publications at the time of writing this report.

Objectives and criteria for evaluation

Primary objectives:

- To determine the maximum tolerated dose (MTD) of AZD2461 as a single agent.
- To determine a recommended Phase 2 dose of AZD2461.

Secondary objectives:

- To characterize the pharmacokinetics (PK) of AZD2461 given as a single agent.
- To evaluate the pharmacodynamic (PD) response after treatment with AZD2461 given as a single agent.
- To explore the clinical tumour response after treatment with AZD2461 given as a single agent.

Study design

This study was a first-time-in-man (FTIM), Phase I, dose-escalation, open-label study of the PARP inhibitor, AZD2461, given as a single agent. Approximately 40 to 75 patients were planned to be enrolled in this study. AZD2461 was administered orally on a daily basis during 21 day cycles.

The initial dose escalation used an accelerated titration scheme, followed by a 3 + 3 dose-escalation design. The initial dosing frequency was once daily, which was to be adjusted (e.g., changed to twice-daily dosing) based on emerging PK and PD data in the first or subsequent cohorts of patients.

Target patient population and sample size

The target population of this trial consisted of male and female patients ≥18 years-of-age with histologically or cytologically confirmed diagnoses of solid tumour malignancies that were not responsive to standard therapies or for which there were no effective therapies.

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

AZD2461 was administered orally as hard capsules at 100, 200, and 400 mg per day.

- 100 mg = 1 capsule per day, Lot#10-004772AZ
- 200 mg = 2 capsules per day, Lot#10-004772AZ
- 400 mg = 4 capsules per day, Lot#10-004772AZ

Duration of treatment

AZD2461 was administered orally on a daily basis during 21-day cycles. Each patient was allowed to continue dosing as long as they were considered to be receiving clinical benefit. Patients 30000001 and 30000004 each received 2 cycles and Patient 30000003 received 6 cycles of treatment.

Statistical methods

Analyses were not performed, because the study was stopped after 3 patients were treated. All data are listed and tabulated.

Patient population

Three Caucasian female patients aged 34, 68, and 69 years were treated in this study. Their primary tumours were breast (2) and colon (1), and their baseline Eastern Cooperative Oncology Group (ECOG) performance status ratings were all zero. These patients were the first in each of Cohorts 1, 2, and 3 (100, 200, and 400 mg AZD2461 daily, respectively). One male patient was a screen failure (Investigator decision).

When the study was stopped, all treated patients were given the option to remain in the trial for as long as they were experiencing a benefit from treatment. Subsequently all patients discontinued treatment due to progressive disease.

Summary of efficacy results

The primary objective of this study was to evaluate the safety and toxicity of AZD2461 and to establish its MTD. Due to the decision to suspend development of AZD2461 after 3 patients were treated, the MTD was not reached.

Patients were assessed for response, with scans at the end of every 2 cycles. All 3 patients discontinued treatment due to disease progression. Of note, one patient continued into

6 cycles of treatment before developing progressive disease, with scans at the end of Cycles 2 and 4 showing "stable disease". The other 2 patients received 2 cycles of treatment.

Summary of pharmacokinetic results

A summary of the AZD2461 PK data is presented in comparison to the PK data from its metabolite (O-desmethyl metabolite), AZ12709846.

There were too few patients to analyse the PK data, but some trends were observed:

- At each dose level (100, 200, and 400 mg), maximum concentration (C_{max}) of AZD2461 was approximately double that of AZ12709846.
- Maximum plasma concentrations of both AZD2461 and its metabolite were achieved rapidly after dosing (typically 2 to 4 hours).
- Plasma half-life (t½) was consistently shorter for AZD2461 compared to AZ12709846.
- Area under the plasma concentration curve (AUC) was consistently higher for AZD2461.
- Although trough concentrations were reported, the data cannot be interpreted in view of the associated sampling and dosing history.

Summary of pharmacodynamic results

Inhibition of poly (ADP-ribose) polymerase (PARP) in peripheral blood mononuclear cells (PBMCs) and in tumour biopsies collected from patients before and after dosing with AZD2461 were planned to be used to support proof of mechanism. The assay was a sandwich enzyme-linked immunosorbent assay (ELISA) followed by chemiluminescence.

The raw poly (ADP-ribose) (PAR) activity data was converted to % inhibition of poly (ADP-ribose) polymerase (PARP) compared to the baseline value. Thus, the calculated % inhibition was dependent on the estimated PAR activity in each baseline sample.

For Patient 30000001, ~30% inhibition of PARP was observed 1 hour after the first dose of the study, but that inhibition was recovered within the 24-hour dosing period (almost recovered to base line by 6 hours). A similar pattern on Day 1 of Cycle 2 was also observed.

For Patient 30000003, the baseline value for PAR activity was much higher. As a result, 80% to 90% inhibition was observed at both 1 and 6 hours post dose on Day 1 of both cycles. Since there was not a 24-hour post-dose sample, it could not be determined whether PARP inhibition was recovering within the dosing interval.

For Patient 30000004, inhibition could not be calculated, because the PAR activity at baseline was lower than in any of the post-dose samples.

Summary of safety results

Patients 30000001 (100 mg per day) and 30000004 (400 mg per day) were each in Cycle 2 of treatment when their disease progressed. Patient 30000003 (200 mg per day) was in Cycle 6 of treatment.

Every patient experienced more than 1 adverse event. Those that were considered treatment-related included diarrhoea (N=2), anorexia (N=1), rash (N=1), nausea (N=1), fatigue (N=1), and anaemia (N=2). A summary of all adverse events is presented in Table 1.

Table 1: Summary of adverse events for each patient by preferred term, arranged by system organ class

SOC/MedDRA Preferred term	Number of events		
	Patient E30000001 100mg/day	**Patient E30000003 200mg/day**	**Patient E30000004 400mg/day**
Number of events	6	10	9
Blood and lymphatic system disorders			
Anaemia	0	0	2
Eye Disorders			
Lacrimation increased	0	1	0
Gastrointestinal disorders			
Nausea	1	1	0
Diarrhoea	1	1	0
General disorders and administration site conditions			
Fatigue	1	0	1
Oedema Peripheral	0	1	0
Pyrexia	0	0	1
Infections and infestations			
Urinary tract infection	0	1	0
Oral herpes	0	0	1
Injury, poisoning and procedural complications			
Ankle fracture	0	1	0

Table 1: Summary of adverse events for each patient by preferred term, arranged by system organ class

SOC/MedDRA Preferred term	Number of events		
	Patient E30000001 100mg/day	Patient E30000003 200mg/day	Patient E30000004 400mg/day
Metabolism and nutrition disorders			
Anorexia	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia	0	0	1
Bone pain	0	0	1
Muscle spasms	1	0	0
Musculoskeletal pain	0	0	1
Nervous system disorders			
Dizziness	0	0	1
Respiratory, thoracic and mediastinal disorders			
Sinus congestion	0	1	0
Renal and urinary disorders			
Dysuria	1	1	0
Micturition urgency	0	1	0
Skin and subcutaneous tissue disorders			
Rash	0	1	0

AE = Adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SOC = System organ class.

There were no deaths, SAEs other than death, discontinuations due to investigational product, or other significant AEs during this study. In addition, no DLTs were reported during the study. All AEs were Grade 1 with the exception of the 2 events of anaemia (same patient) that were Grade 2. The only Grade 3 haematology or clinical chemistry toxicity reported during the study was lymphopenia in a single patient who had CTC Grade 2 lymphopenia pre-treatment. There were no signals of potential drug-induced liver injury (DILI); no patients had liver parameters that met “Hy’s Law” criteria. There were no cases where elevation of ALT over 3 X ULN was associated with subsequent elevation of bilirubin over 2 X ULN and vice versa. There were no clinically meaningful abnormalities in vital signs or ECGs during the trial.

Conclusions