AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1208
Study Code	D4510C00005
Edition Number	1
Date	30 March 2015
EudraCT Number	2012-001944-23

A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD1208 in Patients with Advanced Solid Malignancies including Malignant Lymphoma

Study dates: First patient enrolled: 17 July 2012
Last patient enrolled: 14 April 2014

Phase of development: Phase I

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

Study centres

The study was conducted at 3 centres (2 in UK and 1 in Japan).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The objectives of the study and outcome variables are summarised in Table S1.

Table S1 Objectives and outcome variables

Objective			**Outcome Variable**
Priority	Type	Description	Description
Primary	Safety	To investigate the safety and tolerability of AZD1208 up to a maximum tolerated dose (MTD) and define the dose(s) for further clinical evaluation when given daily to patients with advanced solid malignancies including malignant lymphoma.	Adverse events, laboratory data, vital signs, physical examination, and electrocardiogram changes
Secondary	Pharmaco kinetics (PK)	To characterise the PK of AZD1208 following a single administration and at steady state after multiple dosing when given orally.	Single dose: C_{max}, t_{max}, λz, $t_{1/2\lambda z}$, AUC, $AUC_{(0-24)}$, $AUC_{(0-t)}$, CL/F, V_z/F, MRT, CLR, Ae % dose Multiple dose: $C_{ss\,max}$, $t_{ss\,max}$, $C_{ss\,min}$, AUC_{ss}, CL_{ss}/F, V_{ss} z/F, RAC(AUC), RAC (C_{max}), CLRss, Ae_{ss}, fe $_{ss}$, % dose
	Efficacy	To obtain a preliminary assessment of the anti-tumour activity of AZD1208 by evaluation of tumour response using Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.1 or Revised Cheson Criteria for Malignant Lymphoma.	Best objective response, objective response rate, percent change in tumour size, duration of response
Exploratory[a]	Pharmaco dynamics/ Biomarker	To determine 4β-hydroxycholesterol for exploration of the potential of pregnane X receptor (PXR) induction following AZD1208 treatment.	4β-hydroxycholesterol

[a] Other exploratory biomarkers were reported separate from the clinical study report.

Ae amount of drug excreted unchanged ; Ae_{ss} Ae at steady state; AUC area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-24)}$ AUC from zero to 24 hours; $AUC_{(0-t)}$ AUC from zero to the time of the last measurable concentration; AUC_{ss} AUC from zero to the end of the dosing interval; CL/F apparent plasma clearance; CL_{ss}/F apparent plasma clearance at steady state; CLR renal clearance; $CL_{R,ss}$ renal clearance at steady state; C_{max} maximum plasma concentration; $C_{ss\,max}$ maximum plasma concentration at steady state; $C_{ss\,min}$ minimum plasma concentration at steady state; fe ss fraction of drug excreted unchanged at steady state; MRT mean residence time; t_{max} time to C_{max}; t_{ss} max time to $C_{ss\,max}$; $t_{½}\,\lambda_z$ terminal half-life; V_z/F apparent volume of distribution at terminal phase; $V_{ss\,z}/F$ apparent volume of distribution at steady state; λ_z Terminal rate constant.

Study design

This was a Phase I, open-label, multicentre study of AZD1208, administered orally. The study consisted of 2 parts: Part A: dose escalation and Part B: dose expansion. Patients received a single dose on Day 1, followed by 3 days to 7 days washout period (minimum 72 hours), then once daily multiple dosing was initiated. Once the maximum tolerated dose (MTD) or biologically effective dose (BED) was defined, expansion phase (Part B) was planned to begin at the MTD or lower dose, or the BED, using a dose schedule as determined by the SRC, in order to refine the safety, tolerability, and pharmacokinetics (PK) and/or pharmacodynamics of AZD1208.

The single dose period was defined as Cycle 0, which starts at a single dose on Day 1 until the day before the first dose of multiple dosing. Cycle 1 was a 21-day period from the first dose of multiple dosing. The first cycle of multiple dosing commenced using one of the following dosing schedules: Schedule 1 (once daily continuous dosing; 21-day cycle); Schedule 2 (twice daily dosing for 2 weeks [14 days] followed by 2 weeks [14 days] off the IP; 28-day cycle), or Schedule 3 (depending on the emerging PK and safety profile, additional alternate or intermittent dosing schedules). The dose limiting toxicity (DLT) assessment period consisted of Cycle 0 and Cycle 1.

AstraZeneca considered that the overall benefit/risk profile of AZD1208 as a monotherapy agent in an unselected solid tumour patient population no longer supported continuation of clinical study D4510C00005. Thus, AZD1208 development was terminated on 6 June 2014 before the end of Part A (prior to implementation of schedules other than Schedule 1).

Target subject population and sample size

Male and female patients aged 18 years and above, with a histological or cytological confirmation of a solid malignant tumour, including malignant lymphoma, with at least 1 measurable lesion that could be assessed accurately at baseline and was suitable for repeated assessments, and with a Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, were enrolled in the study.

Approximately, 48 evaluable patients with advanced solid malignancies including lymphoma, were planned to be enrolled in Part A of the study. At least 3 and up to 6 evaluable patients were required for each dose cohort. In Part B it was planned to enrol an additional 12 evaluable patients at a minimum, including at least 6 Japanese patients.

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

AZD1208 was administered orally as capsules of 10 mg, 60 mg, and 100 mg in strength. AZD1208 was manufactured by AstraZeneca. The batch numbers used were 12-002191AZ, 12-002219AZ, 12-003027AZ, 12-003068AZ, 12-003252AZ, 13-000176AZ, 13-000224AZ, 13-001278AZ, 13-001453AZ, D4510C5-1, D4510C5-3, D4510C5-4, D4510C5-5, D4510C5-6, and D4510C5-8.

Duration of treatment

All evaluations during the once daily dosing regimen were conducted as 21-day assessment cycles. Patients received AZD1208 as long as they continued to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria.

Statistical methods

All summary data was presented by initial dose groups (by cohort) and for Schedule 1, Part A.

No hypothesis testing was carried out in this study and as such no formal statistical comparisons were made. Descriptive statistics was generally used and geometric mean and coefficient of variation (CV) were displayed, as appropriate.

Subject population

A total of 43 patients were enrolled, of which 35 patients were treated with AZD1208 between 120 mg to 800 mg. All the 35 (100.0%) patients terminated the study treatment and the study. The terminations were mainly due to 'condition under investigation worsened' (23 [65.7%] patients).

Patient demographics, baseline and disease characteristics were similar in each cohort. Mean overall age was 61.7 years; 48.6% of the patients were male and 51.4% were female. Patients were either of White (54.3%) or Japanese (45.7%) race; all Asian patients were from Japan.

Overall, the study population was representative of the intended target population for this Phase I mixed tumour type study.

Summary of efficacy results

There was no evidence of anti-tumour activity as no patients had a response (complete/partial) according to Response Evaluation Criteria in Solid Tumour (RECIST) assessments RECIST at any time during the study. For the 33 evaluable patients, the best objective response as assessed was stable disease for 13 patients, progression (RECIST/death) for 15 patients; the remaining 5 patients were not evaluable.

Summary of pharmacokinetic results

The PK of AZD1208 was highly variable across the dose of 120 mg to 800 mg with moderate absorption after a single dose of AZD1208. After a single dose, the exposure increased proportional to dose across the dosing interval. Following multiple doses of AZD1208,

absorption was moderate, exposure was highly variable and showed time-dependent PK. Apparent clearance increased with time and duration of dosing leading to decreased exposure with increasing doses.

The 4β-hydroxycholesterol data showed that AZD1208 increased CYP3A4 activity after multiple dosing which likely resulted in increased clearance of AZD1208 (auto induction).

Summary of safety results

The starting dose of 120 mg was selected based on ICH guidelines and the data from the pre-clinical studies. The dose of AZD1208 was escalated to find an MTD in patients with advanced solid malignancies including malignant lymphoma, as defined by DLT. However, an MTD was not established in this study due to the termination of the clinical development of AZD1208.

There were 4 patients who experienced DLTs: 1 patient in the 240 mg cohort (gamma-glutamyl transferase increased, CTCAE Grade 3), 1 patient in the 540 mg cohort (vomiting, CTCAE Grade 3), and 2 patients in the 800 mg cohort (both were fatigue, CTCAE Grade 3). A total of 11 patients had at least 1 dose interruption, while none of the patients had their dose reduced.

All patients experienced AEs and at least 1 AE experienced by each patient was considered causally related to the IP, as judged by the investigator. The majority of the observed AEs were from the SOCs: Gastrointestinal disorders (34 [97.1%] patients), Metabolism and nutrition disorders (28 [80.0%] patients), and Investigations (21 [60.0%] patients). Most AEs reported were of mild to moderate intensity. Diarrhoea, nausea, and vomiting were the most frequently reported AEs, occurring in over 50% of the patients. Sixteen (45.7%) patients had an AE of CTCAE Grade ≥3, of which fatigue (4 [11.4%] patients) was the most common event.

One patient in the 700 mg cohort died due to general physical health deterioration. However, this event was considered not causally related to the IP, as judged by the investigator. There were 8 (22.9%) patients who had an SAE in this study, of these, 1 patient had 3 SAEs (vomiting, fatigue, and general physical health deterioration) that were considered by the investigator to be causally related to AZD1208. There were 4 (11.4%) patients who experienced AEs that led to discontinuation of AZD1208, and the DAEs were considered causally related to the IP, as judged by the investigator.

There were no clinically relevant treatment related changes or trends in any laboratory variables, vital signs, electrocradiograms, and physical examination in patients exposed to AZD1208 during the study.