Clinical Trial Disclosure Synopsis

Drug Substance	AZD1480
Study Code	D1060C00002
Edition Number	1

A Phase I, Open-Label, Multi-Center, Dose-Escalation Study to Assess the Safety and Tolerability and Pharmacokinetics of AZD1480 Administered as Daily Oral Monotherapy in Patients with Advanced Solid Malignancies in the Escalation Phase and EGFR- or ROS-Mutant NSCLC or Non-Smokers with Lung Metastasis in the Expansion Phase

Study dates:	First subject enrolled: 22 April 2010 Last subject last visit: 20 September 2012
Phase of development:	Clinical pharmacology (I)

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

Rationale for early termination of study

As a result of a comprehensive review of the Janus-associated kinase (JAK) 1/2 inhibitor AZD1480 clinical trials data and an expert consultation, AstraZeneca decided to stop the internal and external clinical development of AZD1480. This decision was made after a full review of data from all studies of AZD1480 and a risk-benefit analysis. Therefore, enrollment to all AZD1480 clinical studies was closed. Patients receiving AZD1480, who were receiving benefit, had the option to continue treatment with AZD1480, and continued in follow-up where appropriate as per the Clinical Study Protocol.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 presents the primary and secondary objectives and the outcome variables for this study.

Table S1 Primary and secondary objectives and outcome variables

Objectives		Outcome variables
Priority (Type)	**Description**	**Description**
Primary (Safety)	To investigate the safety and tolerability of AZD1480 when administered as monotherapy in patients with advanced solid malignancies in the escalation phase and EGFR- or ROS-mutant NSCLC or non-smokers with lung metastasis in the expansion phase	AEs, laboratory data (clinical chemistry, hematology, coagulation, and urinalysis testing), vital signs, ECG changes, physical examination, and other safety assessments (eye exam, PFT, chest X-ray, HRCT, and neurological assessments using BARS and MMSE-2)
Secondary (PK)	To characterize the PK of AZD1480 when given orally as monotherapy	Single dose: C_{max}, t_{max}, AUC, $AUC_{(0-24)}$, $AUC_{(0-t)}$, CL/F, V_z/F, $t_{1/2}$ Multiple dose: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $C_{avg,ss}$, $AUC_{\tau,ss}$, $AUC_{(0-t)}$, CL_{ss}/F, V_{ss}/F, $t_{1/2ss}$, R_{AC}, MRT
Secondary (Efficacy)	To obtain a preliminary assessment of the anti-tumor activity of AZD1480 by evaluation of tumor response using RECIST (version 1.1) criteria	Change in tumor size, best overall RR, best objective tumor response, DCR, and DoR
Secondary (PD)	To evaluate the extent of inhibition of pSTAT3 following treatment with AZD1480 alone	pSTAT3 MFI, change in pSTAT3 MFI from baseline, and %change in pSTAT3 MFI from baseline

Results of the exploratory analyses are presented separately from the CSR.
AE Adverse event; AUC Area under the plasma-concentration time curve from time zero to infinity; $AUC_{\tau,ss}$ Area under the plasma concentration-time curve across the dosing interval; $AUC_{(0-t)}$ Area under the plasma-concentration time curve from time zero to time of the last quantifiable concentration; $AUC_{(0-24)}$ Area under the plasma concentration-time curve from time zero to 24 hours; BARS Brief Ataxia Rating Scale; $C_{avg,ss}$ Average predicted drug concentration at steady state; CL/F Total apparent drug clearance; CL_{ss}/F Total apparent drug clearance at steady state; C_{max} Maximum plasma (peak) drug concentration after single dose administration; $C_{max,ss}$ Maximum (peak) drug concentration at steady state; $C_{min,ss}$ Minimum (trough) drug concentration at steady state; CSR Clinical Study Report; DCR Disease control rate; DoR Duration of response; ECG Electrocardiogram; EGFR Epidermal growth factor receptor; HRCT High-resolution computerized

tomography; MFI Mean fluorescence intensity; MMSE Mini-mental state examination; MRT Mean residence time; NSCLC Non-small cell lung cancer; PD Pharmacodynamic; PFT Pulmonary function test; PK Pharmacokinetics; pSTAT3 Phosphorylation of signal transducers and activators of transcription 3; R_{AC} Accumulation ratio; RECIST Response Evaluation Criteria in Solid Tumors; ROS Reactive oxygen species; RR Response rate; $t_{1/2}$ Half-life; $t_{1/2ss}$ Half-life at steady state; t_{max} Time to reach maximum plasma concentration; $t_{max,ss}$ Time to reach maximum plasma concentration at steady state; V_{ss}/F Apparent volume of distribution at steady state after multiple dose; V_z/F Apparent volume of distribution at steady state after single dose.

Study design

This was a Phase I, open-label, multi-center study of AZD1480 administered orally in patients with advanced solid malignancies that are refractory to standard therapy or for which no standard therapy exists in the escalation phase and epidermal growth factor receptor (EGFR)- or reactive oxygen species (ROS)-mutant non-small cell lung cancer (NSCLC) or non-smokers with lung metastasis in the expansion phase. The study consisted of 2 phases: Monotherapy dose escalation and monotherapy safety expansion.

Monotherapy dose escalation phase: This phase aimed to define the maximum tolerated dose (MTD) of AZD1480. Patients received daily dosing of AZD1480 for each 21-day cycle. Safety and available pharmacokinetic (PK) data were assessed by a Safety Review Committee (SRC) prior to dose escalation for the next cohort.

The planned starting oral dose was 10 mg once daily (QD). The QD dosing continued until MTD or an appropriate dose determined by SRC was defined. After the MTD or an appropriate dose was defined for the QD dosing schedule, the dosing could be switched to twice daily (BID) based on the emerging safety data from previous cohorts. This BID dosing was to be continued until the final BID dose was determined.

In this phase, patients received 10 mg QD, 20 mg QD, 40 mg QD, 70 mg QD, 20 mg BID, 30 mg BID, 35 mg BID, and 45 mg BID. A dose was to be considered non-tolerated and dose escalation was to be ceased if ≥33% evaluable patients experienced dose-limiting toxicity (DLT) at any dose level. Once the non-tolerated dose (NTD) was defined, the MTD was to be confirmed at the previous dose level below the NTD, or a dose between the NTD and the last tolerated dose was to be investigated. Six evaluable patients were required to determine the MTD at a given dose level. MTD was to be defined as the highest dose at which <33% of the patients experienced a DLT.

Monotherapy safety expansion phase: This phase was to be initiated only after the final BID dose was determined; however, the study was stopped before the initiation of the dose expansion phase based on a review of the AZD1480 clinical trial data and risk-benefit analysis.

Target subject population and sample size

Patients aged ≥18 years, with a histological or cytological confirmation of a solid, malignant tumor (escalation phase) or EGFR mutation-positive or ROS-translocated NSCLC (expansion phase) that was refractory to standard therapies or for which no standard therapies existed (patients with lymphoma were to be excluded from the expansion phase) were enrolled in the

study. Approximately 30 evaluable patients were to be enrolled in the monotherapy dose escalation phase. At least 3 to 6 evaluable patients were required for each dose cohort. The total number of patients depended upon the number of dose escalations required.

Investigational product and comparators: Dosage, mode of administration, and batch numbers

AZD1480 was administered orally as capsules with dose strengths including 2.5 mg, 10 mg, and 40 mg. Batch numbers for the 2.5 mg capsules were 10-001862AZ, WK90586.001, and WK90586.009. Batch numbers for the 10 mg capsules were 10-001863AZ, WK90586.005, WK90586.002, and WK90586.008. Batch numbers for the 40 mg capsules were WK90586.003, WK90586.004, WK90586.006, and WK90586.007.

Duration of treatment

In the monotherapy dose escalation phase, patients received continuous daily dosing for 21 days in Cycle 1. Patients continued to receive 21-day cycles of AZD1480 after Cycle 1 for as long as they continued to derive benefit from the treatment as judged by the investigator, did not have disease progression, and did not experience any other discontinuation criterion.

Statistical methods

No formal statistical analysis was performed for the study. Descriptive statistics were used to list patient data and, where appropriate, data were summarized. The study was stopped before initiation of the dose expansion phase. Therefore, only the dose escalation phase is reported. Graphical presentations of the data were produced to aid interpretation, where appropriate.

Subject population

A total of 73 patients were enrolled in the dose escalation phase of the study. Of the patients enrolled, 38 patients received at least 1 dose of AZD1480. All patients dosed with AZD1480 discontinued treatment, with the most common reason for discontinuation being worsening of the condition under investigation (27 [71.1%] patients). The majority of patients (35/38 patients) had metastatic disease at baseline. The mean age of the patients in this study was 55.8 years (range: 31 years to 74 years). The majority of patients (24 [63.2%] patients) were female and 34 (89.5%) patients were Caucasian. All 38 patients who received at least 1 dose of AZD1480 were included in the Safety and PK analysis sets.

Summary of efficacy results

No patients in this study had an overall response of complete response (CR) or partial response (PR). Of the 38 patients, 14 (36.8%) patients had a best overall response of stable disease (SD): 1 patient in the 10 mg QD dose cohort, 2 patients in the 20 mg QD dose cohort, 3 patients in the 40 mg QD dose cohort, 4 patients in the 70 mg QD dose cohort, 1 patient in the 30 mg BID dose cohort, 2 patients in the 35 mg BID dose cohort, and 1 patient in the 45 mg BID dose cohort. Nineteen (50%) patients had disease progression and 5 (13.2%) patients were not evaluable for best overall response.

Summary of pharmacokinetic results

Pharmacokinetic analysis revealed that AZD1480 had rapid absorption and elimination. Maximum plasma (peak) drug concentration after single dose administration (C_{max}) was attained ~1 hour post-dose and the half-life of AZD1480 was ~5 hours. There was minimal accumulation after repeated daily QD or BID dosing. The exposure was increased in a dose-dependent manner from 10 mg QD to 45 mg BID. At the 40 mg QD and the 45 mg BID dose levels, the C_{max} reached 1410 µg/L and 1560 µg/L on Day 1, respectively.

Summary of pharmacodynamic results

The mean percentage change from baseline typically showed reductions in the levels of phosphorylation of signal transducers and activators of transcription 3 (pSTAT3), with maximal effect typically seen 1 hour to 2 hours post-dose. The maximum reductions in mean percentage change from baseline in pSTAT3 were observed in the 30 mg BID and the 45 mg BID dose cohorts.

Summary of safety results

The median duration of exposure to AZD1480 was between 28 days and 70 days (range: 13 days to 148 days). There was no apparent difference in exposure between QD and BID dosing or between the different doses. The median relative dose intensity was high in the majority of dose groups: 88.2% in patients treated with 45 mg BID and 100% for all the other dose groups (range: 61.5% to 100%). Sixteen (42.1%) patients experienced an interruption of dose and 7 (18.4%) patients had a dose reduction.

Because of the short half-life of AZD1480 and the need for chronic target suppression, QD dosing was abandoned without reaching the MTD and BID dosing was initiated at 20 mg. The 45 mg BID dose was considered non-tolerable due to neurological and psychiatric events, which, although not meeting the criteria for DLT, were considered non-tolerable in the long term. Therefore, the dose was de-escalated to 35 mg BID, which was also non-tolerable because 2/3 evaluable patients at this dose level had DLTs. Thus, the MTD was not established based on the protocol-defined criteria.

The majority of patients (37 [97.4%] patients) experienced at least 1 adverse event (AE). The most common AEs (reported in ≥20% patients) were fatigue (18 [47.4%] patients), dizziness (11 [28.9%] patients), constipation (9 [23.7%] patients), and abdominal distention (8 [21.1%] patients). The majority of reported events of dizziness (9/11 patients) and one-half of the AEs of abdominal distension (4/8 patients) were assessed by the investigator as being causally related to AZD1480, whereas the majority of reported AEs of fatigue and constipation were not considered by the investigator as being causally related to AZD1480 (5/18 patients and 3/9 patients, respectively). Thirteen (34.2%) patients experienced AEs of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3. The majority of these AEs were isolated and likely reflected a patient population with advanced malignancies.

Nineteen (50%) patients reported neurological AEs and 11 (28.9%) patients reported psychiatric AEs. Despite a clear causal association between AZD1480 and neurological and

psychiatric AEs, no consistent abnormalities were detected on regular neurological assessment. Although the majority of neurologic/psychiatric AEs were of mild or moderate intensity (CTCAE grades 1 and 2), AEs of CTCAE grade 2 were dose limiting as they were not considered tolerable by patients in the long term. Neurological and psychiatric AEs were reported in all dosing cohorts and dose dependency was not apparent; however, patients treated with higher doses and/or BID dosing reported shorter time to the onset of AEs after starting AZD1480, and the clinical picture was more complex. CTCAE grade 3 anxiety in 1 patient in the AZD1480 35 mg BID dosing cohort was considered by the investigator to be causally related to AZD1480.

Seven (18.4%) patients reported ocular AEs of CTCAE grade ≤2 (mild or moderate). Ocular AEs were a part of the complex picture of neurological toxicity associated with AZD1480 and did not suggest a primary effect on the eye. Ophthalmological examination (slit lamp and fundoscopy) did not identify any significant findings.

No CTCAE grade >2 dose-related pulmonary toxicity signal was noted during the study. The only serious adverse event (SAE) and CTCAE grade 3 pulmonary AE was pneumonia, reported by 1 patient in the AZD1480 45 mg BID dose cohort. Although the majority of patients had no significant lung findings on high-resolution computerized tomography, 1 patient in the AZD1480 40 mg QD dose cohort was noted to have scattered ground glass opacity throughout the lungs and pneumonitis (CTCAE grade 2) and also reported dyspnea on exertion (CTCAE grade 2) and lower extremity edema (CTCAE grade 2) 4 weeks after starting AZD1480. Following discontinuation of AZD1480 and diuretic treatment, the fluid retention and ground glass opacity were much improved, but the patient still reported exertional dyspnea. These events were considered as being causally related to AZD1480 by the investigator.

Four patients had DLTs during the study, and all these events were neurological and psychiatric. They were very broad and included dizziness, ataxia, hallucination, and anxiety. At higher doses, patients experienced a combination of neurological and psychiatric events. The majority of those events were mild or moderate (CTCAE grade 1 to 2) in intensity; however, they were not considered tolerable in the long term and were dose limiting.

No AEs with outcome of death were reported in the study. Two patients died due to their underlying malignancy. Less than one-third (10 [26.3%] patients) of the patients experienced SAEs during the study, and the SAE reporting rate did not show dose dependency. The majority of the SAEs were CTCAE grade 3. The investigator assessed SAEs of confusional state in 1 patient and anxiety in another patient as being causally related to AZD1480, which was consistent with the known neurological/psychiatric toxicity of AZD1480. A total of 6 (15.8%) patients discontinued AZD1480 due to an AE. Three patients discontinued AZD1480 due to AEs considered by the investigator as being causally related to AZD1480: 1 patient due to pneumonitis, 1 patient due to muscular weakness and hallucinations, and 1 patient due to anxiety.

No clinically significant changes in hematology laboratory parameters, physical examination, vital signs, or electrocardiogram parameters were observed during the study. One patient

treated with AZD1480 30 mg BID for pancreatic carcinoma reported during the study elevation of aspartate aminotransferase (AST) and bilirubin that met the definition of a potential Hy's law case report. At screening, his alanine aminotransferase (ALT), AST, and alkaline phosphatase (ALP) were slightly elevated (1.5xupper limit of normal [ULN], 1.4xULN, and 2.4xULN, respectively). At baseline, his ALT and AST were within the reference range and his ALP was still high (2.9xULN). The highest recorded AST was 5.1xULN and ALT was 3.5xULN (potentially Hy's law case report); further elevation of ALP and increase in bilirubin during the study did not coincide with AST and ALT elevations, bilirubin particularly increased at the time when the patient reported gastrointestinal hemorrhage. AST and ALT normalized on study treatment and bilirubin and ALP returned to baseline values following the discontinuation of AZD1480. The investigator considered AST, ALT, and ALP elevations to be related to AZD1480, and considered bilirubin elevation as not related to AZD1480.