AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1480
Study Code	D1060C00004
Edition Number	1
Date	15 October 2013

A Phase I, Open-Label, Multi-Center, Dose-Escalation Study to Assess the Safety and Tolerability, and Pharmacokinetics of AZD1480 in Asian Patients with Advanced Solid Malignancies and Asian Patients with Child-Pugh A to B7 Advanced Hepatocellular Carcinoma (HCC) in the Escalation Phase, EGFR or ROS Mutant NSCLC and Non-Smokers with Lung Metastasis and Gastric Cancer and Solid Tumor with Biopsy Available in the Expansion Phase

Study dates: First patient enrolled: 26 November 2010
Last patient last visit: 18 December 2012

Phase of development: Clinical pharmacology (I)

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

Early termination of study

As a result of a comprehensive review of the Janus 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 3 Phase I studies of AZD1480 and an assessment of the current benefit-risk profile, with a particular focus on neurological/psychiatric adverse events (AEs) consistent across all studies and pharmacodynamics data at the various doses in the Phase I program. Therefore, enrolment to all AZD1480 clinical studies was closed. Patients receiving AZD1480, who continued to show clinical benefit, had an option to carry on receiving AZD1480, following detailed information on potential risks, discussion with investigator, and reconsenting. All patients who continued the treatment were followed up according to the protocol. For this study, all the patients discontinued AZD1480 by 18 December 2012.

Objectives and criteria for evaluation

The primary and secondary objectives and the outcome variables for this study are shown 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 AZD1480 when given orally with the study schedule and patient population (see Table S2).	Exposure, AEs, vital signs, ECG parameters, physical examination, laboratory assessments (hematology, clinical chemistry, and urinalysis), and other safety assessments (eye examination, pulmonary function tests, chest X-ray, HRCT scans, and neurological monitoring using BARS and MMSE-2).

Table S1 Objectives and outcome variables

Objective			Outcome variable
Priority	**Type**	**Description**	**Description**
Secondary	PK	To evaluate the PK of AZD1480 following a single oral administration and at steady state after multiple oral dosing in Asian patients.	Single dose: Cmax, tmax, AUC, AUC(0-24), AUC(0-t), CL/F, Vz/F, Vss/F, t1/2, MRT Multiple dose: Cmax,ss, tmax,ss, Cmin,ss, Cavg,ss, AUCτ,ss, AUC(0-t), CLss/F, Vss/F, t1/2ss, RAC, MRT Instead of AUC(0-24), AUC(0-12) was calculated for BID dosing.
Secondary	Efficacy	To obtain a preliminary assessment of the anti-tumor activity of AZD1480 by evaluation of tumor response using RECIST version 1.1.	Change in tumor size, best ORR, best objective tumor response, DCR, and DoR.
Exploratory	Pharmacodynamics/Biomarker	To assess the effects of AZD1480 on a relevant biomarker of pharmacological activity (pSTAT3) and other biomarkers in STAT and related pathways in paired surrogate tissues (peripheral blood) (all parts, mandatory) and paired tumor biopsies (Part A and C only, optional). Potentially, tumor biopsy samples would be used to evaluate AZD1480 PK in tumor.	pSTAT3 and other biomarkers in STAT pathway/signaling.

Table S1 Objectives and outcome variables

Objective			Outcome variable
Priority	**Type**	**Description**	**Description**
Exploratory	Pharmacodynamics/Biomarker	To investigate the effects of AZD1480, on pharmacodynamic biomarkers including, but not limited to, angiogenesis, cell death, invasion, and inflammatory cytokines, as well as possible associations with anti-tumor activity and AEs.	Angiogenesis, cell death, invasion, and inflammatory cytokines.
Exploratory	Pharmacodynamics/Biomarker	To evaluate changes in CTC counts, as well as possible association with anti-tumor activity.	Exploratory blood-borne biomarkers (CTC count).

Note: Four more results of exploratory analyses regarding the contrast-enhanced ultrasound, genetic, hepatitis B and C viral replication, and α-fetoprotein were to be presented separately from the CSR Synopsis; thus not included in this table.
AE Adverse event; AUC Area under the curve; $AUC_{\tau,ss}$ Area under the plasma concentration-time curve across the dosing interval; $AUC_{(0-t)}$ Area under plasma concentration-time curve from time zero to time of the last quantifiable concentration; $AUC_{(0-24)}$ Area under plasma concentration-time curve from time zero to 24 hours; BARS Brief ataxia rating scale; BID Twice daily; $C_{avg,ss}$ 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; CTC Circulating tumor cells; DCR Disease control rate; DoR Duration of response; ECG Electrocardiogram; HRCT High resolution computerized tomography; MMSE Mini-mental state examination; MRT Mean residence time; ORR Objective response rate; PK Pharmacokinetics; pSTAT3 Phosphorylated signal transducers and activators of transcription 3; R_{AC} Accumulation ratio; RECIST Response Evaluation Criteria in Solid Tumors; STAT Signal transducer and activator of transcription; $t_{1/2}$ 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; V_z/F Apparent volume of distribution.

The details of patient population and dosing schedule are provided in Table S2.

Table S2 Patient population and dosing schedule per each part

	Patient population	**Patient number**	**Dosing schedule**
Part A	Solid tumors excluding HCC	18	Daily dosing of AZD1480
Part B	Advanced HCC (Child-Pugh A to B7)	18	BID dosing of AZD1480
Part C	Solid tumors excluding HCC	18	BID dosing of AZD1480
Expansion 1	NSCLC	Up to 14	BID dosing of AZD1480

Table S2 Patient population and dosing schedule per each part

	Patient population	Patient number	Dosing schedule
Expansion 2	Gastric cancer; solid tumor with biopsy available	14	BID dosing of AZD1480

BID Twice daily; HCC Hepatocellular carcinoma; NSCLC Non-small cell lung cancer.

Study design

This was a Phase I, open-label, multi-center, dose-escalation study to assess the safety and tolerability, and pharmacokinetics (PK) of AZD1480 in Asian patients with advanced solid malignancies and Asian patients with Child-Pugh A to B7 hepatocellular carcinoma (HCC) in the escalation phase, epidermal growth factor receptor (EGFR) or reactive oxygen species (ROS) mutant non-small cell lung cancer (NSCLC) and non-smokers with lung metastasis and gastric cancer and solid tumor with biopsy available in the expansion phase.

Part A and C (Dose escalation phase in solid tumors patients, excluding HCC)

This phase was planned to define the maximum tolerated dose (MTD) of AZD1480. Safety and available data was assessed by the Safety Review Committee (SRC) prior to dose escalation for the next cohort. The starting dose of AZD1480 in Part A was 30 mg based on the highest safe dose from ongoing Phase I studies. Patients started daily dosing on Cycle 1, Day 1 (Cycle=21 days).

After the daily dose MTD was defined in Part A, the total daily starting dose for Part C was to be confirmed (or selected) by the SRC for dose escalation with solid tumor patients. Patients received BID dosing (Cycle=21 days) in Part C. As per the recommendation from the SRC, the patients received 30 mg once daily (QD), 50 mg QD, and 70 mg QD in Part A and 20 mg twice daily (BID), 35 mg BID, and 45 mg BID in Part C.

Part B (Dose escalation phase in HCC patients)

The starting dose for HCC patients on Part B was based on the safety of AZD1480 in patients with adequate liver function using the same schedule. After MTD was defined in Part A, the total daily starting dose confirmed (or selected) by SRC for the dose escalation with Child-Pugh A to B7 HCC patients in Part B was 15 mg. Patients received their first dose in Cycle 1, Day 1. No doses were given on Day 2, Day 3, and Day 4 in order to assess the single dose safety and PK in HCC patients. Each cycle lasted 21 days.

As a result from the SRC, the patients received 15 mg BID, 30 mg BID, and 45 mg BID in Part B.

Expansion (Dose expansion phase in EGFR or ROS mutant NSCLC, non-smokers with lung metastasis patients, gastric cancer patients, and solid tumor with biopsy available)

Following the dose escalation phase of the study, additional patients were to be enrolled to an expansion phase of AZD1480, to further assess the safety, tolerability, and PK of AZD1480. In the expansion phase, up to 14 patients with NSCLC and 14 additional patients with gastric cancer or solid tumor with available biopsy, were to be enrolled at the MTD or lower using a dosing schedule determined by the SRC. Patients received BID dosing (Cycle=21 days). Three (3) patients received 30 mg BID of AZD1480 in Part E, expansion phase.

Target subject population and sample size

The target population included male and female Asian patients ≥18 years old with histologically or cytologically confirmed solid malignant tumor refractory to standard therapies or for which no standard therapies existed (Part A and Part C); EGFR or ROS mutant NSCLC and non-smokers with lung metastasis (Expansion 1); gastric cancer or solid tumor with available biopsy (Expansion 2); Child-Pugh liver function status classified as A to B7 and/or advanced or metastatic HCC, unresectable and incurable with ablative therapy or transcatheter arterial chemoembolization, who failed at least 1 prior systemic treatment (Part B). All the patients were required to have Eastern Cooperative Oncology Group performance status 0 to1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 8 weeks.

Approximately, 84 patients were to be recruited into this study; however, the total number of patients were to depend upon the number of dose escalations required during the course of the study.

Investigational product: 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. In Part A, the starting daily dose was 30 mg QD. Once the MTD was defined in Part A, the total daily starting dose of 20 mg BID for Part C was confirmed by the SRC for the dose escalation with solid tumor patients; and for Child-Pugh A to B7 HCC patients in Part B, a total daily starting dose of 15 mg BID was determined. Patients received BID dosing with each cycle lasting 21 days.

The batch numbers for AZD1480 were: 2.5 mg (09-008420AZ, 32357.5, and 32357.9); 10 mg (10-001946AZ, 32357.2, 32357.4, 32357.6, and 32357.8); and 40 mg (10-005051AZ, 32357.1, and 32357.3).

Duration of treatment

Each dosing cycle lasted 21 days. Patients continued to receive AZD1480 as long as they continued to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria.

Statistical methods

No formal statistical analysis was performed for the primary objective of the study. Descriptive statistics were used to list the data and where appropriate, data were summarized. The study was stopped early in the initiation of the dose expansion phase. Therefore, only the dose escalation phase is reported and data from the dose expansion are included in summaries, where appropriate, due to the small number of patients in the expansion phase. Graphical presentations of the data were produced to aid interpretation, where appropriate.

Subject population

The first and last patients were enrolled on 26 November 2010 and 20 September 2012, respectively, and the last patient completed the study on 18 December 2012. All the patients were enrolled at 3 centers in South Korea.

Patients were enrolled in the study as follows: Part A (23 patients), Part B (16 patients), Part C (16 patients), and Part E (9 patients). The number of patients that received treatment were: Part A (17 patients), Part B (12 patients), Part C (15 patients), and Part E (3 patients). All 47 patients who received AZD1480 discontinued the study, with the most common reason for discontinuation being worsening of the condition under investigation; Part A (12 patients [70.6%]), Part B (6 patients [50.0%]), Part C (9 patients [60.0%]), and Part E (1 patient [33.3%]). All 47 patients for respective parts, who received at least 1 dose of AZD1480 were included in the safety and PK analysis sets. The average age (mean [range]) of patients in this study was: Part A (56.2 years [42 years to 70 years]), Part B (56.7 years [30 years to 78 years]), Part C (53.4 years [37 years to 68 years]), and Part E (65.0 years [51 years to 76 years]). The majority of patients were males: Part A (10 patients [58.8%]), Part B (11 patients [91.7%]), Part C (10 patients [66.7%]), and Part E (2 patients [66.7%]). All patients were Asian (other than Chinese and Japanese). Majority of the patients had a metastatic disease at hepatic, lymph nodal, and respiratory sites at baseline.

Summary of efficacy results

No patients in this study had an overall response of complete response (CR) or partial response (PR). For Part A, 2 patients (40.0%) at 50 mg QD and 1 patient (20.0%) at 70 mg QD had stable disease (SD) ≥6 weeks; while 4 patients (100.0%) in 30 mg QD, 3 patients (60.0%) in 50 mg QD, and 4 patients (80.0%) in 70 mg QD had a best overall response of progressive disease (PD). For Part B, 3 patients (60.0%) in 15 mg BID, 2 patients (66.7%) in 30 mg BID, and 3 patients (75.0%) in 45 mg BID had SD ≥6 weeks; while 2 patients (40.0%) in 15 mg BID, 1 patient (33.3%) in 30 mg BID had a best overall response of PD and 1 patient (25.0%) in 45 mg BID was not evaluable for best overall response. For Part C, 2 patients (40.0%) in 20 mg BID and 3 patients (50.0%) in 35 mg BID had a best overall response of SD ≥6 weeks; while 3 patients (60.0%) in 20 mg BID, 2 patients (33.3%) in 35 mg BID, and 1 patient (50.0%) in 45 mg BID had a best overall response of PD. One (1) patient each in 35 mg BID (16.7%) and 45 mg BID (50.0%) was not evaluable for best overall response. For Part E, no patients had SD ≥6 weeks; 2 patients (66.7%) at 30 mg BID had a best overall response of PD and 1 patient (33.3%) was not evaluable for best overall response.

Summary of PK results

AZD1480 was rapidly absorbed with time of maximum concentration (t_{max}) ranged between 0.5 hours to 2 hours for most of the patients. The mean terminal half-life ($t_{1/2}$) was approximately 6 hours, indicating fast elimination. AZD1480 had dose dependent increase among the dose levels tested. At 70 mg QD cohort, the maximum plasma concentration (C_{max}) and area under the concentration-time curve up to 24 hours (AUC_{0-24}) reached 2192 ng/mL and 12370 ng/mL*hour, respectively, on Day 1. The exposure on Day 22 was very similar to the exposure on Day 1, suggesting there was no accumulation after repeated daily dosing.

Summary of pharmacodynamics/biomarker results (pSTAT3 and tumor biopsy)

For all time points and dose cohorts in Part B, Part C, and Part E, the mean percentage change from baseline typically showed reductions in phosphorylated signal transducers and activators of transcription 3 (pSTAT3), with maximal reduction mostly observed around 1 hour to 2 hours post-dose for both, Cycle 1, Day 1 and Cycle 1, Day 8. The maximum reduction in mean percentage change from baseline for Part B 45 mg BID and Part C 35 mg BID cohorts were 69.52% (1 hour post-dose) and 75.52% (2 hour post-dose), respectively, observed at Cycle 1, Day 8.

In all the cases where pre-treatment and post-treatment biopsies were provided, the patients' post-treatment biopsies showed marked reduction in pSTAT3 staining, with both, staining intensity and percentage of cells positive for pSTAT3 decreasing to zero in most post-treatment biopsies. Decreases were seen in tumor cells and stromal cells.

Summary of safety results

The median duration of actual treatment exposure was 1.4 months in the 50 mg QD cohort (Part A) and less than 1 month in all the other treatment cohorts. The longest actual treatment duration of 11.1 months was recorded in the 30 mg QD cohort (Part A); the shortest duration was 0 months in several cohorts both in the QD and the BID dosing regimens. 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 majority of cohorts, 100% in 30 mg and 50 mg QD (range: 17.6% to 100%). In Part A, 1 patient each had a dose interruption in 30 mg QD (20.0%) and 50 mg QD (16.7%), 3 patients (50.0%) had a dose interruption in 70 mg QD, and only 1 patient (16.7%) had a dose reduction in 50 mg QD. In Part B, 3 patients (60.0%) in 15 mg BID, 1 patient (33.3%) in 30 mg BID, and 2 patients (50.0%) in 45 mg BID had a dose interruption but no patient had a dose reduction. In Part C, 4 patients (57.1%) in 35 mg BID and 1 patient (33.3%) in 45 mg BID had a dose interruption; however, no patient had a dose reduction. In Part E, 2 patients (66.7%) had a dose interruption, while none had a dose reduction.

The most common AEs (reported in >50% of patients in any treatment cohort) were: Dizziness (57.1% to100% of patients) in the 70 mg QD cohort (Part A), 35 mg and 45 mg BID cohorts (Part C), and 30 mg BID cohort (Part E); nausea (Part A, 80% of patients in the

30 mg QD cohort and Part C, 66.7% patients in the 45 mg BID cohort); weight gain (Part B, 66.7% of patients in the 30 mg BID cohort); vomiting and anemia (Part E, 66.7% of patients in the 30 mg BID cohort); aspartate aminotransferase and bilirubin elevations (Part B [patients with HCC], 60% of patients in the 15 mg BID cohort); arthralgia (Part C, 60% of patients in the 20 mg BID cohort); and decreased appetite and fatigue (Part C, 57.1% of patients in the 35 mg BID cohort). Dizziness was very common in several dosing cohorts, which is consistent with the known effect of AZD1480 on nervous system. With other common AEs, no clear pattern was observed, either between AZD1480 dose or QD/BID regimens.

Of the 47 patients who received treatment, 27 patients (57.4%) reported neurological AEs and 8 patients (17.0%) reported psychiatric AEs. Despite a clear causal association between AZD1480 and neurological and psychiatric AEs, no consistent abnormalities were detected on regular neurological assessment using mini-mental state examination and brief ataxia rating scale. The majority of neurological/psychiatric AEs were of mild or moderate intensity (Common Terminology Criteria for Adverse Events [CTCAE] grades 1 and 2); except 3 patients (6.4%) who reported AEs with CTCAE grade ≥3 (1 patient committed suicide and 2 patients reported CTCAE grade 3 dizziness). A 60-year-old male patient, treated with AZD1480 15 mg BID (Part B), committed suicide. The patient did not report any neurological or psychiatric AEs during the study. The event was assessed by the investigator as not related to AZD1480. There is insufficient evidence to confirm causal relationship between the event and AZD1480. The neurological/psychiatric 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 response was not apparent; however, the clinical picture in patients treated with higher doses and/or BID dosing was more complex and the time to onset of AEs was shorter.

Overall, 3 patients reported ocular AEs (ocular hyperemia and punctate keratitis each in 1 patient, and eyelid ptosis in a patient with previous history of eyelid disorder) which were of CTCAE grade ≤2 (mild or moderate). Of these, ocular hyperemia was not considered to be causally related to AZD1480 whereas, punctate keratitis and eyelid ptosis were considered to be causally related to AZD1480 by the investigator. Ophthalmological examination (slit lamp, intraocular pressure, and fundoscopy) did not identify any significant findings.

The pulmonary AEs were mostly mild or moderate. The only pulmonary serious adverse event (SAE) of CTCAE grade 3, reported by 1 patient in Part B, 45 mg BID cohort, was dyspnea, which, according to the lung high resolution computerized tomography (HRCT) findings, was probably due to an infection. Four other patients reported SAEs of pneumonia (2 patients in Part A in 70 mg QD cohort, 1 patient in Part B in 30 mg BID cohort, and 1 patient in Part C in 45 mg BID cohort). The HRCT findings in these patients appeared to be consistent with pneumonia rather than interstitial lung disease. The investigators considered the SAEs of pneumonia in 2 patients treated with 70 mg QD as related to AZD1480, whereas others were assessed as unrelated to the study therapy.

Dose-limiting toxicities (DLTs) were reported in 4 patients, 2 patients in Part A, 70 mg QD and 2 patients in Part C; 1 patient each in 35 mg BID and 45 mg BID cohort. In the 70 mg

QD cohort (Part A), 1 patient reported reduced carbon-monoxide diffusing capacity (CTCAE grade 1), which met an initial DLT definition of "Lung criteria changes." Carbon monoxide diffusion capacity decreased >20% from baseline. The other patient in this cohort (70 mg QD) reported pneumonia (CTCAE grade 2). 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 15 mg. In Part C, 1 patient reported dizziness (CTCAE grade 3) in the 45 mg BID cohort and another patient had diarrhea (CTCAE grade 3) in the 35 mg BID cohort. MTD, as defined by the protocol, was not reached.

Due to neurological and psychiatric events, AZD1480 was not tolerated long-term at 30 mg, 35 mg, and 45 mg BID. Neurological/psychiatric AEs did not meet the criteria for DLT and were mostly mild or moderate (CTCAE grade 1 to 2), however, they were broad, included dizziness, delirium, hallucination, anxiety, major depression, and at higher doses, the patients experienced a combination of these AEs.

The majority of the patients (all patients [100%] in Part A, Part C, and Part E, while 91.7% patients in Part B) experienced AEs. Non-serious AEs were more frequent than SAEs; SAEs were reported by 3 patients (17.6%), 5 patients (41.7%), 5 patients (33.3%), and 1 patient (33.3%) in Part A, Part B, Part C, and Part E, respectively. AEs with CTCAE grade ≥3 were reported in 4 patients (23.5%), 6 patients (50.0%), and 7 patients (46.7%) in Part A, Part B, and Part C, respectively. In Part C and Part E, AZD1480 was discontinued due to AEs in 2 patients (13.3%) and in 1 patient (33.3%), respectively, who received AZD1480 30 mg BID, 35 mg BID, and 45 mg BID. The AEs that led to discontinuation (illusion, diarrhea, and dizziness) were considered as related to AZD1480 by the investigator.

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