AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4877
Study Code	D2782C00006
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A Phase I, Open-label, Multi-center, Dose-escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD4877 Administered Twice a Week in Adult Patients with Advanced Solid Malignancies Including Lymphoma

Study dates: First subject enrolled: 17 April 2007
Last subject last visit: 11 December 2008

Phase of development: Clinical Pharmacology (I)

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

Publications

An abstract of preliminary results of this study has been published:
Stephenson JJ, Lewis N, Martin JC, Ho A, Li J, Wu K, et al. Phase I multicenter study to assess the safety, tolerability, and pharmacokinetics of AZD4877 administered twice weekly in adult patients with advanced solid malignancies. J Clin Oncol 2008;26(15)(Suppl):2516 (abstr).

Early termination of study

In December 2008, it was decided that the expansion recruitment target of 20 patients was no longer feasible since only 4 patients in 6 months had been recruited for the study. The statistical plan was reviewed, and it was determined that a sufficiently robust decision for efficacy could be made based on data from 10 patients. A decision was made on 24 April 2009 to discontinue the study due to ongoing recruitment difficulties. The study was not terminated for safety reasons.

Objectives and criteria for evaluation

The primary and secondary objectives and outcome variables for this study are shown in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
To identify a maximum tolerated dose (MTD) of AZD4877 on a schedule of twice a week for 2 weeks out of every 3 weeks by assessment of the incidence of dose-limiting toxicities (DLTs).	Incidence of DLTs during the 21-day Cycle 1 in Part A
Secondary	**Secondary**
To evaluate the safety and tolerability of AZD4877 by assessment of Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) grade and type of adverse event (AE), changes in laboratory values, vital signs, and incidence of protocol-defined dose modifications or omissions.	Incidence and types of DLTs during Part A; during Parts A & B: study drug exposure; incidence and types of AEs, deaths, serious adverse events (SAEs), discontinuation of treatment with investigational product due to AE (DAEs), other significant adverse events (OAEs); maximum CTCAE grade for AEs; incidence of worst CTCAE grade for lab variables; vital signs and weight changes; categorical summaries of PR, QT, QTcF, and QTcB on ECGs; CTCAE grade for left ventricular ejection fraction (LVEF) on echocardiograms; WHO Performance Status; dose intensity
To determine the pharmacokinetic (PK) parameters of C_{max}, C_{24h}, AUC, $AUC_{(0-24)}$, $t_{½}$, MRT, and V_{ss} of AZD4877 for the twice-a-week schedule.	Obtained from Cycle 1: C_{max}, C_{24h}, AUC, $AUC_{(0-24)}$, $t_{½lz}$, MRT, V_{ss}
Dose expansion (Part B only): To estimate efficacy of AZD4877 through evaluation of objective response rate (ORR), progression-free survival (PFS), and disease control rate (DCR) in patients with B-cell non-Hodgkin lymphoma using the revised response criteria for malignant lymphoma (Cheson et al. J Clin Oncol 2007;25:579-86).	ORR, PFS, DCR

AE Adverse event; AUC Area under the concentration-time curve; $AUC_{(0–24)}$ Area under the concentration-time curve 0 to 24 hours; C_{24h} Plasma concentration at 24 hours; C_{max} Maximum plasma concentration; CTCAE Common Terminology Criteria for Adverse Events; DAE Discontinuation of treatment with investigational product due to AE; DCR Disease control rate; DLT Dose-limiting toxicities; ECG Electrocardiogram. LVEF Left ventricular ejection fraction; MRT Mean residence time; OAE Other significant adverse events; ORR Objective response rate; PFS Progression-free survival; PK Pharmacokinetic; QTcB QTc with Bazett correction; QTcF QTc with Fridericia correction; SAE Serious adverse events. $t_{1/2}$ Elimination half-life; V_{ss} Volume of distribution (apparent) at steady state; WHO World Health Organization.

Exploratory objectives

In addition to the primary and secondary objectives, there were several exploratory objectives that related to Parts A and/or B (see Study Design), as described below. Samples were collected for several of these exploratory objectives, as well as the optional exploratory objective; however, with the exception of Exploratory Objective 7 (presence of monoasters), analyses of Exploratory Objectives 1, 3, 4, 5, 6, and 8 will be reported separately from this study report. Note that for Exploratory Objective 2, individual tumor measurements were not collected in Part A; rather, investigator assessments were provided. Also, data for Exploratory Objectives 3, 4, and 5 are included in the listings of the Clinical Study Report (CSR).

1. To examine the relationship between neutropenia and plasma exposure of AZD4877 by evaluation of appropriate pharmacokinetic (PK) and hematological parameters.

2. Dose escalation (Part A only): To seek preliminary evidence of the anti-tumor activity of AZD4877 by assessing tumor size changes using Response Evaluation Criteria in Solid Tumors (RECIST). Tumor reduction that does not meet criteria for complete or partial response will be noted. Changes in non-measurable tumor will also be noted.

3. Dose expansion (Part B only): To seek preliminary evidence of the anti-tumor activity of AZD4877 in B-cell non-Hodgkin's lymphoma (NHL) by assessing tumor size change assessed as percentage change in sum of the product of the long and short axis diameters (SPD) for measurable disease.

4. Dose expansion (Part B only): To seek preliminary evidence of the anti-tumor activity of AZD4877 by assessing percentage change in 2-[F-18]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) tumor standardized uptake value (SUV_{max}) in patients with FDG-PET–avid B-cell NHL.

5. Dose expansion (Part B only): To estimate efficacy of AZD4877 through evaluation of FDG-PET response rate (RR) in patients with FDG-PET–avid B-cell NHL.

6. To correlate tumor biologic characteristics and clinical outcome by evaluation of exploratory markers of mitosis and the spindle checkpoint, centrosome/ploidy status, mitotic index, and P-glycoprotein (P-gp) expression obtained from tumor samples with anti-tumor activity, safety, and PK parameters.

7. To seek preliminary evidence of mechanism of action in circulating hematopoietic cells by assessing the presence of monoasters.

8. To seek preliminary evidence of mechanism of action by plasma markers of epithelial cell death.

Optional exploratory objective

The objective was to obtain a blood sample for DNA extraction and subsequent, retrospective pharmacogenetic analysis in consenting patients.

Study design

This was an open-label, multi-center study consisting of 2 parts. Part A was a Phase I, dose-escalation study to determine the maximum tolerated dose (MTD) and explore the safety, tolerability, and PK of AZD4877 when administered on Days 1, 4, 8, and 11 during the first 14 days, followed by a 1-week rest period in patients with advanced solid malignancies, including lymphoma. During Part A, each of the following doses of AZD4877 was tested in a cohort of at least 2 evaluable patients: 2, 4, 7, 11, and 15 mg/day. The MTD was defined as

the maximum dose at which no more than 1 patient in a cohort of 6 evaluable patients experienced a dose-limiting toxicity (DLT). A DLT was defined as: Grade 3 or 4 non-hematological toxicity; Grade 4 hematological toxicity (neutropenia ≥4 days, thrombocytopenia) or Grade 3 or 4 neutropenia complicated by ≥38.5°C fever; Grade 3 or 4 hemolysis; Grade 2 diarrhea ≥4 days despite aggressive outpatient management; Grade 3 or 4 diarrhea despite aggressive anti-diarrhea therapy; Grade 3 or 4 vomiting >24 hours despite suitable anti-emetics; or if 2 of the scheduled 4 doses in the first cycle are omitted due to neutropenia.

Part B was designed to examine the efficacy of the MTD when administered to patients with B-cell NHL on the same schedule as in Part A, and to further characterize the safety, tolerability, PK, and pharmacodynamic (PD) effects of AZD4877.

Target patient population and sample size

Part A (dose escalation) of this study enrolled patients ≥18 years of age with histologically or cytologically confirmed solid malignancy (including lymphoma without marrow involvement) that was recurrent metastatic or unresectable and for which standard curative or palliative measures did not exist or were no longer effective. Enrollment was to continue until MTD was identified; it was estimated that 24 patients would be enrolled into Part A. Part B (dose expansion) enrolled patients ≥18 years of age who had B-cell NHL that was refractory to, or who were not eligible for, curative therapy, or who had relapsed following first-line therapy, including stem cell transplant. In addition, patients were to have at least 1 measurable lesion ≥1.5 cm in the longest diameter in the transverse plane on computed tomography (CT). Approximately 20 patients were planned for enrollment into Part B; it was anticipated that approximately 15 of these patients would have FDG-PET–avid disease at all sites at baseline.

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

AZD4877 concentrate (5 mg/mL) was diluted in 0.9% sodium chloride to ensure a concentration <0.4 mg/mL; it was administered as a 1-hour IV infusion. The Formulation Number for this open-label investigational product was F13438; the Batch Numbers were P/4158/19 and P/4158/25A.

Duration of treatment

Following the completion of the 21-day Cycle 1 during the dose-escalation or dose-expansion phases, patients could receive consecutive treatment cycles based on protocol-defined criteria for continuation and withdrawal. Patients who withdrew from study treatment were to be followed up for safety up to 30 days, when possible, after last administration of AZD4877.

Statistical methods

Statistical analyses were restricted to summaries of all data from all dosed patients to assess safety, tolerability, PK, PD, and initial indications of efficacy in patients with solid tumors and in patients with B-cell NHL. Clinically significant changes from baseline were assessed for

vital signs, ECGs, and laboratory safety variables. Due to the early termination of Part B and the small sample size, no formal statistical analyses of objective response rate (ORR), progression-free survival (PFS), FDG-PET response rate (RR), or any other efficacy variables were conducted.

Patient population

A total of 29 patients were enrolled in this study, of whom 22 received at least 1 dose of study treatment (safety analysis set). Of these 22 patients, 18 patients comprised the 5 dosing cohorts included in the dose-escalation phase in Part A (3 patients in the 2-mg group; 3 patients in the 4-mg group; 3 patients in the 7-mg group; 7 patients in the 11-mg group; and 2 patients in the 15-mg group), and 4 patients were included in the dose-expansion phase in Part B.

Twenty patients in the safety analysis set, including 2 patients from Part B, were evaluable for DLTs. Of the 2 patients who were not evaluable, 1 patient discontinued the study due to an SAE of biliary obstruction and the other discontinued due to SAEs of anorexia and dehydration. All 3 of these events were related to lack of therapeutic response and were not related to study drug treatment as assessed by the investigator. Both patients discontinued the study during Cycle 1 after receiving 3 doses of study drug.

In Part A, 16 of the 18 patients were evaluated for RECIST response, while the 2 remaining patients did not have any post-baseline RECIST assessments. The 4 patients enrolled in Part B were evaluated by Cheson criteria rather than by RECIST.

Patients in the safety analysis set (n=22) had a mean age of 61.5 years (range: 44 to 77 years). Most patients were <65 years of age (14 patients), and the majority were white (20 patients). More men (13 patients) than women (9 patients) participated in the study. All patients had relapsed or refractory disease, with a broad representation of primary tumor types in Part A, including colon/colorectal (5 patients), breast (4 patients), bladder (2 patients), and prostate (2 patients) as the most common. All 4 patients in Part B had B-cell NHL. The primary tumor type/histology for the 4 patients was the following: 1) lymph node/mantle cell lymphoma; 2) head and neck/diffuse large B-cell lymphoma; 3) colon/diffuse large B-cell lymphoma; and 4) retroperitoneal/diffuse large B-cell lymphoma. The most common reason for discontinuation from the study was a lack of therapeutic response. No major protocol deviations occurred during the study.

Summary of pharmacokinetic results

Twenty-one patients had evaluable PK data obtained after dose administration on Day 1 of Cycle 1. The PK parameters of AZD4877 are presented in Table S2.

Table S2 Pharmacokinetic parameters of AZD4877 after dose administration on Day 1 of Cycle 1: Geometric mean (CV%)

Parameter	Treatment (n) Geometric mean (CV%)											
	n	2 mg (n=3)	n	4 mg (n=3)	n	7 mg (n=3)	N	11 mg (Part A) (n=7)	n	11 mg (Part B)[a] (n=3)	n	15 mg (n=2)
C_{max} (ng/mL)	3	34.2 (86.0)	3	93.1 (133)	3	98.1 (95.8)	6	89.8 (122)	2	47.1 (35.5)	1	238 (NC)
C_{24h} (ng/mL)	2	1.93 (13.2)	3	7.22 (946)	3	7.66 (73.0)	6	6.83 (59.0)	2	6.67 (118)	1	16.3 (NC)
AUC (ng*h/mL)	1	175 (NC)	1	887 (NC)	1	502 (NC)	4	573 (81.7)	1	296 (NC)	0	NC (NC)
$AUC_{(0-24h)}$ (ng*h/mL)	3	173 (248)	3	611 (247)	3	362 (56.2)	6	376 (58.9)	2	289 (54.4)	1	820 (NC)
$t_{1/2}$ (h)[b]	0	NC (NC)	1	7.2 (NC)	1	19.5 (NC)	4	16.5 (3.51)	1	16.2 (NC)	0	NC (NC)
MRT (h)	1	27.3 (NC)	1	6.42 (NC)	1	22.6 (NC)	4	18.5 (16.1)	1	18.9 (NC)	0	NC (NC)
V_{SS} (L)	1	311 (NC)	1	29.0 (NC)	1	315 (NC)	4	63.1 (9164)	1	704 (NC)	0	NC (NC)

[a] One patient in the 11-mg (Part B) group was not evaluable for PK.
[b] Arithmetic mean (standard deviation) is presented for $t_{1/2}$ (h).
AUC Area under the concentration-time curve; $AUC_{(0–24)}$ Area under the concentration-time curve time 0 to 24 hours; C_{24h} Plasma concentration at 24 hours; C_{max} Maximum plasma concentration; CV Coefficient of variation; MRT Mean resonance time; n Number of patients; NC Not calculated; $t_{1/2}$ Elimination half-life; Vss Volume of distribution (apparent) at steady state.

Over the dose ranges studied (2 to 15 mg), systemic exposure (C_{max} and AUC) of AZD4877 generally increased with dose. The $t_{1/2}$ and V_{ss} values were quite variable (2- to 4-fold), although the data were consistent with previous studies and are probably a consequence of the limited PK data.

Summary of safety results

In the safety analysis population, median duration of exposure was 32 days (range: 4 to 333 days; sum total of 1267 days). The median number of cycles received was 2 (range: 0 to 16 cycles; sum total of 66 cycles) and the median total dose administered was 72 mg (range: 16 to 514; sum total of 2128 mg). Dose intensity as a percentage of the intended dose

administered during Cycle 1 was 100% in all groups, with the exception of the 11-mg Part A group (96.4%) and the 15-mg group (75.0%). During Cycle 2, all groups received 100% of intended dose, except for the 15-mg group (73.3%). One patient in the 4-mg group (Patient E0006001) was incorrectly recorded as receiving 0.4 mg, instead of the actual dose of 4 mg during Cycle 2. For Cycles 3 and 4, all groups (2 mg, 4 mg, 7 mg, 11 mg [Part A], and 11 mg [Part B]) received 100% of intended dose. Dose reductions or omissions occurred only in the 11-mg and 15-mg groups.

The MTD for AZD4877 was identified as 11 mg. Grade 4 neutropenia that occurred in 2 patients at the 15-mg dose level during Cycle 1 was the only DLT reported during the study.

Eighteen patients had at least 1 adverse event. The most common adverse events were fatigue (8 patients), nausea (8 patients), neutropenia (5 patients), and dyspnea (5 patients). Ten patients had adverse events that were considered by the investigator to be causally related to treatment. Neutropenia was the most clinically significant, causally related toxicity.

Table S3 presents the Common Terminology Criteria for Adverse Events (CTCAE) (Version 3.0) Grade ≥3 adverse events by preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA; Version 12.0) for the 11 patients who reported these events. Five of these patients had CTCAE Grade ≥3 adverse events that were considered by the investigator to be causally related to treatment.

Table S3 CTCAE Grade ≥3 adverse events, by MedDRA-preferred term

Variable	Dose (n)						
	Total (N=22)	2 mg (n=3)	4 mg (n=3)	7 mg (n=3)	11 mg (Part A) (n=7)	11 mg (Part B) (n=4)	15 mg (n=2)
Patients with any AE of CTCAE grade ≥3	11	1	1	0	3	4	2
Neutropenia	5	0	0	0	2	1	2[a]
Sepsis	2	0	0	0	0	2[b]	0
Anorexia	2	0	0	0	0	1	1
Pneumonia	1	0	0	0	0	0	1
Hypoxia	1	0	0	0	0	0	1
Pleural effusion	1	0	0	0	0	1	0
Pulmonary embolism	1	0	1	0	0	0	0
Dehydration	1	0	0	0	0	1	0
Chills	1	0	0	0	1	0	0
Bile duct obstruction	1	0	0	0	1	0	0

Table S3 CTCAE Grade ≥3 adverse events, by MedDRA-preferred term

Variable	Dose (n)						
	Total (N=22)	2 mg (n=3)	4 mg (n=3)	7 mg (n=3)	11 mg (Part A) (n=7)	11 mg (Part B) (n=4)	15 mg (n=2)
Hydronephrosis	1	1	0	0	0	0	0

[a] Two patients had neutropenia that was also considered a DLT.
[b] One of these 2patients had an event of sepsis that began 8 days before the first dose of AZD4877 was given; this event resolved by the time the first dose was given.
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events (Version 3.0); DLT Dose-limiting toxicity; MedDRA Medical Dictionary for Regulatory Activities (Version 12.0); N Total number of patients; n Number of patients in treatment group.
Note: A patient could have more than 1 Grade ≥3 adverse event.

Six patients died due to disease progression during the study; none of these deaths were related to an adverse event. Eight patients reported serious adverse events, of which the most common were sepsis (1 event occurring in each of 2 patients in the 11-mg group) and neutropenia (1 event occurring in each of 2 patients in the 15-mg group). The 2 events of neutropenia were considered by the investigator to be causally related to study treatment. Two patients discontinued the study because of adverse events (bile duct obstruction and chills for 1 patient, anorexia for the other patient); none of these events were considered by the investigator to be causally related to study treatment.

Assessment of laboratory results showed that reversible neutropenia and leukopenia occurred in 5 and 4 patients, respectively. Additionally, 2 patients had anemia and 1 patient had thrombocytopenia. No elevations in plasma hemoglobin values were observed. Other laboratory abnormalities that occurred were consistent with those typically found in a population of patients with cancer. No clinically significant treatment-emergent changes in vital signs or ECGs were reported.

Summary of efficacy/anti-tumor results

In Part A, of the 16 patients who were evaluated for RECIST best objective response, no patient demonstrated complete or partial response. Five patients were considered to have stable disease, of which 3 patients had stable disease ≥12 weeks (maximum of 340 days), based on the investigator's assessment of visit response. The majority of patients (n=10) had progressive disease. One patient with NHL in Part A was reported by the investigator to have a response per Cheson criteria. However, only RECIST assessments were collected in Part A and this patient was reported as having a best objective response of stable disease.

In Part B, no patient demonstrated complete or partial response. Two patients had overall best response by Cheson criteria of stable disease as reported by the investigator. The other 2 patients were not evaluable.

Summary of pharmacodynamic activity

Sixteen of 18 patients dosed in Part A had samples obtained for the presence of monoasters (2 mg, n=3; 4 mg, n=2; 7 mg, n=3; 11 mg, n=6; 15 mg, n=2). In patients dosed with 7 mg or less (n=8), no patients had monoasters detected at either 6-8 hours or 24-hours post-dose. In patients dosed with 11 mg, 2 patients had monoasters detected at both 6-8 hours and 24 hours post-dose. At 15 mg, 2 patients had monoasters detected 6-8 hours post-dose, of which 1 also had monoasters detected 24 hours post-dose. No patients in Part B had samples obtained for monoasters.