AstraZeneca

**Clinical Study Report Synopsis**

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# A Phase I, Open-Label, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD4877 Administered Weekly in Japanese Adult Patients with Advanced Solid Malignancies

**Study dates:** First patient enrolled: 8 January 2008
Last patient completed: 25 June 2009

**Phase of development:** Clinical pharmacology (I)

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

## Study centre

This study was conducted at a single center in Japan. The first patient was enrolled on 8 January 2008, and the last patient completed the study on 25 June 2009.

## Publications

None at the time of writing this report.

## Objectives

The primary objectives of this study were:

- To evaluate the safety and tolerability of AZD4877 on a weekly schedule in Japanese patients with advanced solid malignancies
- To determine the PK profile of AZD4877 on a weekly schedule in Japanese patients with advanced solid malignancies

The secondary objective of this study was:

- To identify a maximum tolerated dose (MTD) of AZD4877 on a weekly schedule in Japanese patients with advanced solid malignancies

The exploratory objectives of this study were:

- To examine the relationship between neutropenia and plasma exposure of AZD4877 on a weekly schedule in Japanese patients with advanced solid malignancies (not addressed in this Synopsis)
- To seek preliminary evidence of the anti-tumor activity of AZD4877 on a weekly schedule in Japanese patients with advanced solid malignancies
- To correlate tumor biologic characteristics and clinical outcome in Japanese patients with advanced solid malignancies (not addressed in this Synopsis)

Optional: In consenting patients, to obtain a blood sample for DNA extraction for subsequent, retrospective pharmacogenetic analysis (not addressed in this Synopsis)

## Study design

This was a Phase I, open-label, dose-escalation study to evaluate the safety, tolerability and pharmacokinetics of AZD4877 given intravenously (IV) weekly to Japanese patients with advanced solid malignancies. Each of the following doses of AZD4877 was tested in a cohort of at least 3 evaluable patients: 10, 15, 20 and 25 mg. Dosing decisions and dose escalation decisions for subsequent cohorts of patients were based on protocol-defined safety and tolerability criteria. The MTD was identified as the highest dose at which no more than 1 patient out of 6 experienced DLT during Cycle 1.

**Target patient population and sample size**

The target population included 30 Japanese patients with advanced solid malignancies for which standard curative or palliative measures did not exist or were no longer effective, with at least 3 evaluable patients enrolled in each dose cohort.

**Investigational product: dosage, mode of administration and batch numbers**

AZD4877 Concentrate (5 mg/mL) was diluted in 250 or 500 mL 0.9% sodium chloride to ensure a concentration <0.4 mg/mL; it was administered as a 1-hour IV infusion. One batch (batch number: P/1458/25B) of AZD4877 was used in this study.

**Duration of treatment**

Following the completion of the 28-day Cycle 1, patients could receive consecutive treatment cycles, based on protocol defined criteria for continuation and withdrawal.

**Criteria for evaluation - pharmacokinetics and efficacy (main variables)**

PK variables: $C_{max}$, AUC, $C_{24h}$, $AUC_{(0-24)}$, CL, $t_{1/2\lambda z}$, MRT and $V_{ss}$ following Cycle 1 Day 1 dose. Efficacy variables: investigator assessment of overall best response per RECIST.

**Criteria for evaluation - safety (main variables)**

Primary safety variables: assessment of adverse events, vital signs, haematology, clinical chemistry, urinalysis, and electrocardiogram for safety and tolerability.

**Statistical methods**

Because of sample size limitations, statistical analysis was restricted to summaries of all data from all dosed patients to assess safety, tolerability, PK and initial indications of anti tumor activity of AZD4877. Clinically significant changes from baseline were assessed for vital signs, weight, ECG, laboratory safety variables, and anti-tumor activity.

**Subject population**

Among 21 Japanese patients enrolled in this study. Three failed screening and the remaining 18 were given at least 1 dose of study treatment (3 in 10 mg cohort, 3 in 15 mg cohort, 6 in 20 mg cohort , and 6 in 25 mg cohort). The median age of the 18 patients was 63.5 years (range: 45 to 75 years) and 11 (61.1%) were female. The patients were with various types of tumors in which the cancers of lung (n=6) and breast (n=3) were prominent. All had the metastatic lesions. The seventeen out of 18 patients discontinued the study treatment due to lack of therapeutic response and 1 patient was withdrawn from the study due to AE.

There was no important protocol deviation. Safety evaluation and PK analysis were completed in all 18 patients. Sixteen patients also completed the evaluation of efficacy (2 patients were excluded as they had no target lesion at baseline).

**Summary of pharmacokinetic results**

The geometric mean systemic exposure to AZD4877 in Japanese subjects, as evaluated by the co-primary PK variables ($C_{max}$, AUC, and $C_{24h}$) and the secondary endpoint $AUC_{0-24}$, increased with dose in an approximately dose-proportional manner for the 10 and 15 mg cohorts. However, more than dose proportional increases in those PK variables were seen when compared the 20 mg cohort to the 10 mg cohort. In addition, it appears that those PK variables approximately remained unchanged between 20 mg and 25 mg cohorts.

The geomean AZD4877 clearance (CL) were approximately same (22.4, 22.3 and 19.5 L/h) for the 10, 15 and 25 mg cohorts. However the geomean CL for the 20 mg cohort was slightly lower (14.0 L/h). The geomean AZD4877 half-life ($T_{1/2}$) for the 15 mg, 20 mg and 25 mg cohorts were approximately same (20.3, 21.3, and 21.1 h). However the geomean $T_{1/2}$ for the 10 mg was slightly longer (28.7 h). The geomean AZD4877 mean residence time (MRT) for the 15, 20 and 25 mg cohorts were also approximately same (22.9, 22.4 and 22.2 h). However, the geomean MRT for the 10 mg cohort was longer (34.2 h). For the secondary PK parameters Vss, the 10 mg cohort also had higher values compared to other cohorts.

The apparent variability in the PK parameters with dose may, in part, reflect the small number of patients in each cohort.

Although, the number of patients per group are small for the 10 and 15 mg dose groups (n=3), also for the 20 and 25 mg dose groups (n = 6), PK parameters for Japanese patients appear to be comparable to those reported for Western patients (Study D2782C00001).

**Summary of efficacy results**

None experienced complete or partial response, however, six had an overall best response of "stable disease" (2 in 10 mg cohort, 1 in 15 mg cohort, and 3 in 20 mg cohort), of which the longest treatment duration persisted up to 129 days (18.4 weeks). One patient (20 mg cohort) had stable disease duration ≥12 weeks.

**Summary of safety results**

All 18 patients treated in this study experienced at least one AEs with the total of 168 events, among which 114 events were considered the study drug related by investigators. The most commonly reported AEs (number[%] of patients) were fatigue (39%), nausea (39%), pyrexia (33%), diarrhoea (28%), dizziness (28%), rash (28%), constipation (22%), nasopharyngitis (22%), insomnia (22%).Most of them were mild or moderate (CTCAE grade 1 or 2). AEs with CTCAE grade ≥3 were seen in 3 patients given the 20 mg or higher doses: Neutropenia (CTCAE grade 4) in 20 mg cohort (Patient E0001008), Febrile neutropenia (CTCAE grade 4) in 25 mg cohort (Patient E0001017), and Constipation, Fatigue, Urinary tract infection, and Anorexia (CTCAE grade 3) in 25 mg cohort (Patient E0001014).

Three patients experienced SAEs: Neutropenia (CTCAE grade 4) in 20 mg cohort (Patient E0001008), Febrile neutropenia (CTCAE grade 4) in 25 mg cohort (Patient E0001017) and Constipation, Fatigue, Urinary tract infection (CTCAE grade 3) in 25 mg cohort (Patient

E0001014). One patient discontinued study treatment due to an AE (Cystitis, CTCAE grade 2). No death occurred in this study.

Twelve patients (1 in 10 mg cohort, 1 in 15 mg cohort, 4 in 20 mg cohort, 6 in 25 mg cohort) experienced CTCAE grade ≥3 abnormal laboratory findings/vital signs (number[%] of patients); Neutropenia (56%), Leukopenia (44%), Lymphopenia (6%), Thrombocytopenia (6%), Blood sodium decreased (6%), Haemoglobin decreased (6%), Lymphocyte count decreased (6%), Weight decreased (6%). There were no other clinically relevant changes in clinical laboratory parameters, clinically relevant trends in vital signs, WHO performance status, physical findings, or ECG observations. The higher dose seems to increase the risk of CTCAE grade ≥3 neutropenia (33% each in 10 and 15 mg cohort, 50% in 20 mg cohort, 83% in 25 mg cohort). This study showed no evidence that AZD4877 increases cardiac risk or risk of hemolysis.

Two patients experienced DLTs; one patient (E0001008) in 20 mg cohort with neutropenia and the other (E0001017) in 25 mg cohort with febrile neutropenia, thus the number of patients in both the 20 mg and 25 mg cohorts was expanded to 6.

Although the Secondary Objective(s) of the study called for defining the MTD through DLT occurrence, because CTCAE grade ≥3 neutropenia was seen in 5 of 6 patients enrolled at the 25 mg dose cohort, and a parallel US study (D2782C00001) demonstrated dose-limiting neutropenia at the 30 mg dose level, it was decided that 25 mg would be the recommended phase 2 dose. As such, this study did not escalate to MTD as defined by DLTs, but rather stopped after completing the 25 mg dose cohort.