AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4877
Study Code	D2782C00010
Edition Number	1
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A Phase II, Single Arm, Single Agent, Multicentre, Adaptive 2-Stage Study to Evaluate the Efficacy, Safety and Pharmacokinetics of AZD4877 Administered Weekly in Patients with Recurrent Advanced Urothelial Cancer

Study dates: First patient enrolled: 29 May 2008
Last patient completed: 11 January 2010

Phase of development: Therapeutic exploratory (II)

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

Study centers

This study was conducted at 23 study sites in 5 countries: United States (7 centers), United Kingdom (6 centers), Germany (5 centers), Canada (3 centers), and Spain (2 centers).

Publications

None at the time of writing this report.

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 assess the effect of AZD4877 on the objective response rate (ORR) in patients with recurrent advanced urothelial cancer receiving AZD4877 at the selected dose level of 25 mg once weekly, with response including complete response (CR) or partial response (PR) as assessed by Response Evaluation Criteria In Solid Tumours (RECIST)	ORR: Proportion of patients with measurable tumor CR, or PR according to RECIST and confirmed at least 4 weeks later.
Secondary	**Secondary**
To describe the efficacy of AZD4877 in terms of disease control rate (DCR: CR, PR, and durable stable disease [SD]), duration of objective tumour response (DoR), progression-free survival (PFS) and overall survival (OS)	DCR: The proportion of patients with CR, PR, or SD lasting at least 8 weeks from the first administration of study drug. DoR: Among patients with CR or PR, time from first documentation of CR or PR, whichever occurred earlier, to progression or death. PFS: Time from the first administration of study drug to disease progression or death. OS: Time from the first administration of study drug to death.
To evaluate the pharmacokinetics (PK) of AZD4877 in urothelial cancer patients by C_{max}	Calculation of C_{max} on Days 1 and 8.
To evaluate the safety and tolerability of AZD4877 by assessment of adverse events (AE), changes in laboratory values, vital signs and incidence of protocol-defined dose modifications or omissions	Study drug exposure; incidence and types of AEs, deaths, SAEs, and DAEs; maximum CTCAE Grade for AEs; laboratory assessments; vital signs changes; and categorical summaries of QT, QTcF, and QTcB on ECGs.
Exploratory	**Exploratory**
To estimate the individual AZD4877 PK parameters by a population PK modelling approach	No efficacy variables were derived to support this objective.[a]

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
To examine the relationship between AZD4877 exposure (C_{max}) and appropriate efficacy and safety endpoints by descriptive plots or PK/PD modelling analysis	No efficacy variables were derived to support this objective.[a]
Optional: In consenting patients, to correlate tumour biological characteristics with clinical outcome, safety and PK parameters by evaluation of exploratory biomarkers of mitosis, centrosome/ploidy status, mitotic index, P-gp expression or other proteins/genes implicated in the cell cycle or pathways important to the development of cancer, in archived tumour samples	No efficacy variables were derived to support this objective.[a]

AE Adverse event; Cmax Maximum plasma (peak) drug concentration after single-dose administration; CR Complete response; CTCAE Common Terminology Criteria for Adverse Events (Version 3.0); DAE Discontinuation due to an adverse event; DCR Disease control rate; DoR Duration of response; ECG Electrocardiogram; ORR Objective response rate; OS Overall survival; PD Pharmacodynamic; PFS Progression-free survival; PK Pharmacokinetic; PR Partial remission; QTcB QTc Bazett; QTcF QTc Fridericia; RECIST Response Evaluation Criteria In Solid Tumours; SAE Serious adverse event; SD Stable disease.

[a] The study was terminated early for lack of efficacy after preliminary assessment of the response data from the first 20 patients. Therefore, no exploratory efficacy variables were derived programmatically.

Study design and early termination criteria

This was a Phase II, single-arm, single-agent, multicenter, adaptive 2-stage study to evaluate the efficacy, safety, and PK of AZD4877 administered weekly in patients with recurrent advanced transitional cell carcinoma of the urothelium (bladder, renal pelvis, ureter, or urethra; mixed histology permitted) that was not amenable to curative surgery and/or radiotherapy. Treatment was to continue until disease progression, death, unacceptable toxicity, or withdrawal. Patients who withdrew from the study were followed up for safety, where possible, for up to 30 days after last administration of AZD4877.

The design of this study was based on objective response rate (ORR) observed in evaluable patients. Enrollment in the study was to stop if 2 or fewer responses were seen after data were reviewed for 20 evaluable patients (Stage 1). The study protocol permitted continued recruitment into Stage 2 while awaiting assessment of response in the first 20 patients. If at least 3 responses were seen in the first 20 evaluable patients, recruitment was to continue until it was confirmed that an additional 20 evaluable patients had been entered (Stage 2).

Per protocol, the efficacy data from the first 20 evaluable patients in this study were analyzed for ORR to AZD4877 to arrive at a decision to either continue or stop enrollment into the study. None of the first 20 evaluable patients had a confirmed CR or PR; therefore, the decision was made to terminate enrollment into the study on 16 January 2009. The study was not terminated for safety reasons.

Target population and sample size

This study enrolled patients with recurrent, advanced urothelial cancer after failure with a maximum of 2 prior chemotherapy regimens (1 of which had been given in the adjuvant or neo-adjuvant setting) for advanced, unresectable, or metastatic disease.

A minimum of 20 and a maximum of 40 evaluable patients were required. An evaluable patient was defined as a patient who met all inclusion/exclusion criteria and who had received at least 1 dose of AZD4877. Allowing for 20% non-evaluable patients, up to 50 patients were expected to be enrolled. The study design had at least 86% power to rule out ORR of 10% or less in favor of ORR of 25% or more at a 1-sided significance level of 10%.

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

AZD4877 25 mg was administered as a 1-hour intravenous infusion on a weekly schedule, for 3 weeks out of each 4-week cycle.

The Formulation Number for this open-label investigational product was F13438; the Batch Numbers were P/4158/19 and P/4158/25A.

Statistical methods

Due to early termination of the study, no formal statistical analyses for the primary and secondary outcome variables were conducted. Statistical analyses were restricted to summaries of all data from all patients who received at least 1 dose of AZD4877 to assess safety, tolerability, PK biomarker, and initial indications of activity of AZD4877. Clinically significant changes from baseline were assessed for laboratory, vital signs, and ECG variables.

Patient population

Fifty-four patients with recurrent, advanced urothelial cancer were enrolled in the study. Of these, 41 patients received at least 1 dose of AZD4877 and were evaluable for safety, 39 patients were evaluable for response by RECIST criteria (excluding 2 patients who had baseline scans performed more than 28 days before dosing), and 33 patients were evaluable for PK assessments (8 patients did not have post Cycle 1, Day 1 PK samples and were thus excluded from the analysis). All dosed patients discontinued AZD4877.

Patients in the safety analysis set (n=41) had a mean age of 63.7 years (range: 36 to 87 years). Of these, 17 (41.5%) patients were 18 to <65 years of age, 19 (46.3%) patients were ≥65 to <75 years of age, and 5 (12.2%) patients were ≥75 years of age (n=5). The majority of patients (40 [97.6%] patients) were Caucasian, and 1 (2.4%) patient was black/African American. More men (30 [73.2%] patients) than women (11 [26.8%] patients) participated in the study.

Most patients (26 [63.4%] patients) entered the study within 6-36 months after initial diagnosis. Twenty-eight (68.3%) patients had locally advanced disease at entry (26 patients to 1-2 sites, and 2 patients to 3-6 sites; the number of sites for the remaining 15 patients was

unavailable). Thirty-six (87.8%) patients had metastatic disease at entry (21 patients to 1-2 sites, and 15 patients to 3-6 sites; the number of sites for the remaining 5 patients was unavailable).

These findings are representative of a general population with urothelial cancer.

Summary of efficacy results

Of the 39 patients evaluable for response by RECIST criteria, 1 (2.6%) patient had a partial response to AZD4877. No patient had a complete response.

Seven patients had a best objective response (BOR) of stable disease ≥8 weeks (including 1 [2.6%] patient with unconfirmed partial response). Twenty-nine (74.4%) patients had BOR of progressive disease.

Twenty-five (61.0%) patients were alive, and 5 (12.2%) patients were progression free, at 16 weeks. Seven (17.1%) patients were alive at 32 weeks.

The median overall survival for this study was 23.1 weeks (range: 1.3 to 48.1 weeks). The median progression-free survival was 7.3 weeks (range: 0 to 44 weeks).

Summary of pharmacokinetic results

Thirty-three patients had evaluable PK data. Geometric mean C_{max} at Day 1 was 138 ng/mL (CV% 74.6) and at Day 8 was 144 ng/mL (CV% 109), which is consistent with other AZD4877 clinical studies utilizing the same dose and schedule.

Summary of safety results

During the study, the median number of days of exposure was 43 days (range: 1 to 309 days). A median of 2 cycles were initiated (range: 1 to 12 cycles), with a median of 2 cycles completed (range: 0 to 11 cycles). A median of 5 doses were administered (range: 1 to 23 doses), with a median total exposure of 100 mg (range: 25 to 505 mg).

Mean dose intensity during each cycle, as a percentage of intended dose (mg) administered, was the following: Cycle 1, 76.6% (41 patients); Cycle 2, 69.2% (32 patients); Cycle 3, 80.7% (10 patients); Cycle 4, 67.5% (8 patients). These findings are consistent with previous AZD4877 studies utilizing the same dose and schedule.

All 41 patients in the safety analysis set had at least 1 AE. The most commonly reported AEs (occurring in ≥10% of patients) by Medical Dictionary for Regulatory Activities (Version 12.1; MedDRA) were neutropenia (24 [56.1%] patients), urinary tract infection (13 [31.7%] patients), fatigue (13 31.7%] patients), anemia (11 [26.8%] patients), nausea (11 [26.8%] patients), constipation (8 [19.5%] patients), vomiting (8 [19.5%] patients), leukopenia (7 [17.1%] patients), pyrexia (7 [17.1%] patients), anorexia (7 [17.1%] patients), abdominal pain (6 [14.6%] patients), dyspnea (6 [14.6%] patients), diarrhea (5 [12.2%] patients), asthenia

(5 [12.2%] patients), back pain (5 [12.2%] patients), insomnia (5 [12.2%] patients), and weight decreased (5 [12.2%] patients).

Twenty-nine (70.7%) patients had CTCAE Grade ≥3 AEs, of which 25 (61.0%) patients had had events that were considered by the investigator to be causally related to treatment. Table S2 presents the CTCAE Grade ≥3 AEs that occurred in 2 or more patients by MedDRA preferred terms.

Table S2 CTCAE Grade 3 or higher adverse events occurring in 2 or more patients, by MedDRA-preferred term (safety analysis set)

AE of CTCAE Grade ≥3[a]	Number (%) of patients (N=41)
Neutropenia	21 (51.2)
Leukopenia	4 (9.8)
Dyspnea	2 (4.9)
Fatigue	2 (4.9)
Ureteric obstruction	2 (4.9)
Urinary tract infection	2 (4.9)

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events (Version 3.0); MedDRA Medical Dictionary for Regulatory Activities (Version 12.1); n Number of patients in the treatment group.

[a] Patients could have had more than 1 Grade ≥3 adverse event.

Of the 41 patients dosed with AZD4877, 24 (58.5%) patients died during the study. Twenty-one (51.2%) patients died from disease progression. Three (7.3%) patients had fatal serious adverse events (SAEs) during the study: 1 (2.6%) patient had congestive heart failure as primary cause and acute myocardial infarction as a secondary cause (both considered by the investigator to be related to study drug treatment), 1 (2.6%) patient who had a urinary tract infection, and 1 (2.6%) patient who had unknown cause of death (considered by the investigator to be related to study drug treatment).

A total of 14 (34.1%) patients reported SAEs. The only SAEs that occurred in more than 1 patient were urinary tract infection and dehydration, which were reported by 2 (4.9%) patients each. Four (9.8%) of the 14 patients with SAEs had events that were considered by the investigator to be causally related to study drug treatment (neutropenia, dehydration, and leucopenia in 1 patient; acute myocardial infarction and congestive heart failure in 1 patient; abdominal pain and dehydration in 1 patient; and death [cause unknown] in 1 patient).

Five (12.2%) patients discontinued taking AZD4877 due to AEs (1 patient with CTCAE Grade 2 rash; 1 patient with CTCAE Grade 3 dyspnea; 1 patient with CTCAE Grade 5 acute myocardial infarction [considered by the investigator to be related to study drug treatment]; 1

patient with ureteral obstruction; and 1 patient with ventricular arrhythmia. One additional patient who died of a cause unknown discontinued taking AZD4877 and discontinued from the study due to the event. Another patient discontinued the study due to an AE of CTCAE Grade 2 opioid intoxication.

Twenty-eight (68.3%) patients had CTCAE Grade 3 or 4 laboratory values. The majority of the Grade 3 or 4 events were low neutrophils and leukocytes. The abnormalities that occurred were consistent with those typically found in a population of patients with recurrent advanced urothelial cancer. No clinically significant treatment-emergent changes in vital signs or ECGs were noted.