AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4877
Study Code	D2782C00001
Edition Number	1
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A Phase I, Open-Label, Dose-Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD4877 Administered Weekly in Patients with Advanced Solid Malignancies

Study dates: First patient enrolled: 26 September 2006
Last patient completed: 26 September 2008

Phase of development: Clinical Pharmacology (1)

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

Study centers

This study was conducted at 3 sites in the United States. The first patient was enrolled on 26 September 2006, and the last patient completed the study on 26 September 2008.

Publications

An abstract of preliminary results of this study has been published:
Infante JR, Spratlin J, Kurzrock R, Eckhardt G, Burris H, Puchalski T et al. Clinical, pharmacokinetic (PK), pharmacodynamic findings in a Phase I trial of weekly (wkly) intravenous AZD4877 in patients with refractory solid tumors. J Clin Oncol 26: 2008 (May 20 suppl; abstract 2501).

Objectives

The primary objectives of this study were as follows:

- To identify a maximum tolerated dose (MTD) of AZD4877 on a weekly schedule by assessment of the incidence of dose-limiting toxicities (DLTs)
- Determine the PK parameters of C_{max}, AUC and C_{24h} of AZD4877 for the weekly schedule

The secondary objectives of the study were as follows:

- 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 AE, changes in laboratory values, vital signs, and incidence of protocol defined dose modifications or omissions
- Determine the PK parameters of $AUC_{(0-t)}$[1], CL, $t_{1/2\lambda z}$, MRT and V_{ss} of AZD4877 for the weekly schedule obtained during Cycle 1

The exploratory objectives of this study were as follows:

- To examine the relationship between neutropenia and plasma exposure of AZD4877 by evaluation of appropriate PK and hematology parameters
- To seek preliminary evidence of the anti-tumor activity of AZD4877 by assessing tumor changes using Response Evaluation Criteria in Solid Tumors (RECIST).

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[1] The protocol stated that the secondary variable $AUC_{(0-t)}$ would be derived. This was replaced by $AUC_{(0-24)}$ because it was considered a more comparable measure of exposure across patients and doses.

Tumor reduction that did not meet the criteria for partial regression was noted. Changes in non-measurable tumor were also noted.

- To seek preliminary evidence of mechanism of action (1) in circulating hematopoietic cells by assessing the presence of monoasters and (2) by plasma markers of epithelial cell death ([2] not addressed in this Synopsis)

- 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-gp expression obtained from archived tumor samples with anti-tumor activity, safety, and PK parameters (not addressed in this Synopsis)

Optional: 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, first-time-in-man, open-label, multi-center, dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics (PK) of AZD4877, given weekly. The study consisted of 2 parts: the Dose Escalation phase and the Dose Expansion phase. During the Dose Escalation phase of the study, each of the following doses of AZD4877 was tested in a cohort of at least 3 evaluable patients: 5, 7.5, 10, 15, 20, 30, 36, and 45 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 patients ≥18 years with solid malignancy, including non-Hodgkin lymphoma, without marrow involvement, that was metastatic or unresectable and for which standard curative or palliative measures did not exist or were no longer effective. An enrollment of approximately 50 patients was anticipated, with at least 3 patients enrolled in each dose cohort during Dose Escalation and at least 12 during Dose Expansion.

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. Five batches of AZD4877 were used in this study. Individual batch numbers are included in the Clinical Study Report.

Duration of treatment

Following the completion of the 28-day Cycle 1 during the Dose Escalation or Dose Expansion phase, 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, V_{ss} following Cycle 1 Day 1 dose. Pharmacodynamic (PD) variables: change from baseline in absolute neutrophil count (ANC) during Cycle 1; presence of monoasters (exploratory). Efficacy variables: investigator assessment of overall best response per RECIST; number of patients with stable disease ≥12 weeks.

Criteria for evaluation - safety (main variables)

Primary safety variable: incidence of DLTs during Cycle 1 in both the Dose Escalation and Dose Expansion phases. Additional safety variables: incidence of adverse events (AEs); deaths, serious adverse events (SAEs), discontinuation of treatment with investigational product due to AE (DAEs); 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; dose modifications/omissions categories; dose intensity.

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, PD, 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

A total of 51 patients were enrolled in this study and 43 of these received at least 1 dose of study treatment. Of these 43 patients, 29 comprised the 9 dosing cohorts included in the Dose Escalation phase, and 14 were included in the Dose Expansion phase. The dosed patients had a mean age of 61.2 years (range: 39 to 83 years). Thirty-six (83.7%) dosed patients were White and 27 (62.8%) were men. All patients had metastatic disease, with a broad representation of primary tumor types, including bladder, pancreatic, and colon as the most common. The most common reason for discontinuation was lack of therapeutic response.

Summary of pharmacokinetic results

The systemic exposure to AZD4877, as evaluated by C_{max}, AUC, and C_{24h}, and AUC_{0-24}, increased with dose in an approximately dose-proportional manner. The terminal elimination half-life ranged in individual patients from 9 to 21 hours, with a geometric mean of 16.2 hours across all patients investigated. Results support an approximately linear PK of AZD4877.

Summary of pharmacodynamic results

Monoaster formation, an indicator of Eg5 inhibition, was observed in at least 1 patient at each of the following doses: 7.5, 10, 20, 25, 30, 36, and 45 mg.

Summary of pharmacokinetic/pharmacodynamic relationships

The data suggest that severity of neutropenia correlates with increasing drug exposure, with the relationship between maximum percent decrease in ANC and PK parameters described by an Emax or a sigmoid Emax relationship.

Summary of efficacy results

There were 41 patients in the Patients Evaluated for RECIST Response Analysis Set. None of these patients experienced complete or partial response. Eleven patients had an overall best response of "stable disease" per investigator assessment, which ranged in duration up to 46.6 weeks. Seven patients had stable disease of ≥12 weeks; 6 of these 7 patients received 20 mg per dose or more. There was no trend in the type of cancer that demonstrated stable disease.

Summary of safety results

The MTD for AZD4877 was identified as 30 mg. The most common DLT during Cycle 1 and overall was neutropenia. Due to the frequency of dose reductions and omissions as a result of neutropenia experienced by patients at the 30-mg dose level and the reduced number of omissions and reductions at the 20-mg dose level, an intermediate dose of 25 mg was selected for the Dose Expansion phase of this study. An additional factor in the decision to select an intermediate dose was the inability to distinguish the 30-mg and 20-mg doses on the basis of available PK data; ie, exposure appeared to be similar for both doses.

All patients had at least 1 AE. The most common AEs were neutropenia (58%), fatigue (44%), nausea (35%), and constipation (30%). Neutropenia was the most clinically significant, causally related toxicity; the majority of Grade ≥3 AEs were neutropenia. There were 4 deaths: 3 due to disease progression; 1 due to an acute myocardial infarction (not causally related). The most common SAEs were neutropenia (26%; most considered causally related) and constipation (7%). There were 4 DAEs, and none were causally related. This study showed no evidence that AZD4877 increases cardiac risk or risk of hemolysis.

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