AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6244
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A Phase II, Open, Randomised Study to Assess the Efficacy and Safety of AZD6244 vs. Capecitabine (Xeloda™) in Patients with Advanced or Metastatic Pancreatic Cancer, who have Failed First-line Gemcitabine Therapy (Gemzar™)

Study dates:	First patient enrolled: 01 August 2006 Last patient enrolled: 25 January 2008
Phase of development:	Therapeutic exploratory (II)

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

Study centre(s)

Fifteen centres in 5 countries (Australia, Bulgaria, Hungary, Romania and the United States [US]) recruited patients into the study. The first patient was enrolled into the study on 01 August 2006.

Publications

None at the time of writing this report.

Objectives

Primary objective

The primary objective of this study was to assess the efficacy of AZD6244[1] versus capecitabine (Xeloda™) in the treatment of advanced or metastatic pancreatic cancer by assessment of time to death (TTD).

Secondary objectives

The secondary objectives of the study were:

- To assess efficacy of AZD6244 versus capecitabine in the treatment of advanced or metastatic pancreatic cancer by assessment of disease progression.
- To assess the safety and tolerability of AZD6244 in the treatment of advanced or metastatic pancreatic cancer by review of adverse events (AEs) and laboratory parameters.

Study design

This was a Phase II, multi-centre, open, randomised, 2-arm, parallel-group study in patients with advanced or metastatic pancreatic cancer who had failed first-line gemcitabine therapy (Gemzar™). Patients were randomised in a 1:1 ratio to receive either AZD6244 or capecitabine.

Target patient population and sample size

Patients who were at least 18 years of age with confirmed pancreatic cancer, a World Health Organisation performance status of 0 to 2, a life expectancy of more than 12 weeks, who had failed first-line gemcitabine therapy and who were considered suitable for treatment with capecitabine were eligible. Patients who had received previous therapy with an epidermal growth factor receptor inhibitor or mitogen activated protein kinase kinase inhibitor or had failed prior capecitabine therapy were not eligible. Use of capecitabine short-term (about

[1] ARRY-142886 (now referred to as AZD6244) was discovered by Array BioPharma and is licensed by AstraZeneca Pharmaceuticals for clinical development and commercialisation in the field of oncology.

6 weeks) as a radiation sensitizer, or in the adjuvant setting provided there was disease control for at least 3 months, was allowed.

A total of 38 death events would ensure the study had at least 80% power to detect a true hazard ratio (HR) of 0.5 at the 2-sided 20% significance level. Therefore, a result from this Phase II study would be considered to be statistically significant if the 2-sided p-value was <0.2. Assuming median survival of 3 months for capecitabine, recruitment of 64 patients in 8 months was expected to yield approximately 38 death events, approximately 3 months after the completion of recruitment.

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

AZD6244 (50 mg and 100 mg) was supplied by AstraZeneca as a crystalline solid for reconstitution with an aqueous Captisol® diluent. Nine batches of AZD6244, 7 batches of capecitabine and 6 batches of Captisol® were used in this study. Individual batch numbers are included in the clinical study report (CSR).

A dispersion of AZD6244 100 mg was administered orally twice-daily (BD), prior to breakfast and the evening meal. If patients were unable to tolerate AZD6244 100 mg BD, then a dose reduction initially to AZD6244 50 mg BD and then 50 mg once-daily was allowed. Dose reductions below 50 mg once-daily were not allowed. Once the dose had been reduced it was not to be increased again.

The comparator, capecitabine (1250 mg/m^2), was administered orally BD for 2 weeks followed by a 1-week rest period given as 3-weekly cycles. Doses of capecitabine were individualised as required by the capecitabine prescribing information. Dose reductions were allowed as part of routine clinical practice. Capecitabine was to be administered with food.

Duration of treatment

Patients received (investigational product [IP]; AZD6244 100 mg BD or capecitabine 1250 mg/m^2 BD) until objective and/or clinical progression, provided they were deriving clinical benefit, in the absence of unacceptable toxicity and provided the patient was willing to continue in the study.

Criteria for evaluation – efficacy (main variables)

The primary outcome variable for efficacy was assessed by comparing TTD between AZD6244 and capecitabine on an intent to treat basis (ITT).

The secondary objective of assessing the efficacy of AZD6244 versus capecitabine was made by comparing the number of patients with a progression event occurring on or before mandatory tumour assessment visit (MTAV). This was defined as the earliest of:

- Objective and/or clinical disease progression as measured using response evaluation criteria in solid tumours (RECIST) criteria, or
- Death from any cause

All patients (including those previously withdrawn from treatment) had an MTAV if they did not already have confirmed disease progression.

In addition, the date of disease progression and the investigators opinion of the patient's best overall response were collected based on tumour assessments conducted according to the site standard clinical practice.

Criteria for evaluation - safety (main variables)

There were no formal statistical analyses for the secondary safety objective (AEs, clinical chemistry and haematology). The treatment groups were compared descriptively using summary statistics and percentage counts.

Statistical methods

The TTD (days) was calculated as the interval from date of randomisation to date of patient death (from any cause). Patients who had not died at the time of the final analysis were censored at the last date the patient was known to be alive.

The analysis for survival was performed using a Cox proportional hazards regression model on an ITT basis. The model allowed for the effect of treatment, which was estimated using the HR, together with the corresponding confidence interval (CI) and p-value. TTD was also summarised using the Kaplan-Meier method which presented estimates of TTD by treatment group.

The number of patients with progression events occurring on or before the scheduled time-point (MTAV) was compared between the treatment groups using a logistic regression model with a complementary log-log function and including a factor for treatment group. The results were approximated as a HR. The estimated HR of progression event occurring in patients treated with AZD6244 compared with capecitabine was reported with CI and p-value.

The MTAV for this study was 27 February 2008 (±3 days). Data cut-off for survival occurred on 05 April 2008.

The ITT population (N=70) was represented by all randomised patients categorized by randomised treatment arms. The evaluable for safety (EFS) population (N=69) was all patients who received at least 1 dose of trial medication. Patients were analysed according to the trial medication actually received.

Subject population

- Sixty-four patients were planned. Eighty-seven patients were enrolled into this study and 70 patients were randomised to treatment; of these, 69 (99%) patients received IP.

- Thirty-eight and 32 patients were randomised to the AZD6244 group and capecitabine group respectively. One patient in AZD6244 group was excluded from the EFS analysis set because they were randomised to the study but did not receive IP.

- Thirty-two (84%) patients in the AZD6244 group and 29 (91%) patients in the capecitabine group had discontinued IP on or before the data cut-off; the primary reason for discontinuation of IP was condition under investigation worsened (disease progression).

- Eight (11%) patients were ongoing in the study at the time of data cut-off (5 [13%] patients in the AZD6244 group and 3 [9%] patients in the capecitabine group).

- The 2 treatment groups were generally comparable for demographic characteristics. However, there was a gender imbalance; 24 (63%) patients in the AZD6244 group were male compared with 11 (34%) patients in the capecitabine group.

Summary of efficacy results

- The primary outcome variable was TTD, 21 (55%) patients in the AZD6244 group, compared with 19 (59%) patients in the capecitabine group died on or before the data cut-off for survival (05 April 2008) (ITT population). The median TTD was 164 days and 152 days in the AZD6244 and capecitabine groups, respectively. There was no statistically significant difference between the 2 treatment groups in TTD (HR 1.03, 2-sided 80% CI: 0.68, 1.57; p=0.92). Data for the EFS analysis set were in general consistent with the ITT population. The gender imbalance did not affect the primary endpoint (TTD) under analysis in this study.

- The secondary outcome variable was progression event count, 32 (84%) patients in the AZD6244 group compared with 28 (88%) patients in the capecitabine group had a disease progression event as of the MTAV (27 February 2008) (ITT population). The resulting HR was 0.89 (2-sided 80% CI: 0.60, 1.31; p=0.69). This difference was not statistically significant at the pre-defined significance level of $p<0.2$. Data for the EFS analysis set were in general consistent with the ITT population.

- The median time to first disease progression event was 63 days in the AZD6244 group compared with 68 days in the capecitabine group (ITT population). The analysis of progression free survival (PFS) gave a HR of 1.24 (2-sided 80% CI: 0.88, 1.75, p=0.41). This difference was not statistically significant at the pre-defined significance level of p<0.2.

  – It should be noted that the protocol did not require regular tumour assessments, so it possible that time to progression may be overstated for some patients. Further, the frequency of assessment may have differed between the treatment arms, thus, the stated HR may not be a fair reflection of the comparative PFS.

- In the ITT analysis set, 5 patients (2 patients in the AZD6244 group and 3 patients in the capecitabine group) achieved a best overall response of partial response to treatment as defined by the investigator.

  – Please note, tumour response was not an endpoint in this study and a single assessment of partial response was accepted as a best overall response of partial response.

  – Best overall response was not assessed robustly in this study.

Summary of safety results

- At the time of data cut-off (05 April 2008) for this CSR, median total exposure to AZD6244 and capecitabine was 63 days and 62 days, respectively.

- In total, 19 (51%) patients in the AZD6244 group and 16 (50%) patients in the capecitabine group experienced AEs that led to dose reduction, dose interruption or permanent discontinuation of treatment.

- Thirty-five (95%) patients in the AZD6244 group and 30 (94%) patients in the capecitabine group experienced at least 1 AE; 32 (86%) patients and 21 (66%) patients experienced AEs considered by the investigator to be related to AZD6244 or capecitabine treatment, respectively. Dermatitis acneiform, diarrhoea, and vomiting were the most common AEs reported with AZD6244 therapy. The AEs of nausea, palmar-plantar erthrodysaesthesia syndrome, and diarrhoea that were the most commonly reported AEs with capecitabine are consistent with the Summary of Product Characteristics for capecitabine. Most AEs were of Grade 1 (mild) or 2 (moderate) events.

- Of the 69 patients who received IP in this study, 2 (5%) patients had fatal serious AEs (SAEs) in the AZD6244 group by data cut-off, each due to pulmonary embolism. Neither event was considered to be related to AZD6244 treatment.

- The only SAEs reported by more than 1 patient in either treatment group were bacterial sepsis (2 [5%] patients in the AZD6244 group) and pulmonary embolism (2 [5%] patients in the AZD6244 group and 2 [6%] patients in the capecitabine group).

- During the study, 2 (5%) patients in the AZD6244 group and 4 (13%) patients in the capecitabine group had an AE leading to the permanent withdrawal of IP. No AE that led to permanent withdrawal of a patient from treatment was observed in more than 1 patient.

- No new safety concerns for AZD6244 were identified from the clinical laboratory results.