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| Drug Substance(s) | AZD6244 | **SYNOPSIS** | (For national authority use only) |
| Study Code | D1532C00012 | | |
| Date | 21 January 2008 | | |

# A Phase II, Open, Randomised Study to Assess the Efficacy and Safety of AZD6244 vs pemetrexed (Alimta®) in Patients with Non-Small Cell Lung Cancer who Have Failed One or Two Prior Chemotherapeutic Regimens

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First patient enrolled** | 22 August 2006 | Therapeutic exploratory (II) |
| **Last patient enrolled** | 8 May 2007 | |

## Objectives

The primary objective of this study was to assess the efficacy of AZD6244 versus pemetrexed (ALIMTA®) in the second or third-line treatment of advanced non-small cell lung cancer (NSCLC) by assessment of disease progression.

The secondary objective of the study was to assess the safety and tolerability of AZD6244 in the treatment of NSCLC 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, to assess the efficacy and safety of the mix and drink formulation of AZD6244 free-base in patients with advanced NSCLC cancer who had failed 1 or 2 previous chemotherapeutic regimens.

Patients received either:

- AZD6244 100 mg administered orally twice daily (BD) as the mix and drink formulation, or
- Pemetrexed 500 mg/m$^2$ administered by IV infusion over 10 minutes every 3 weeks.

The mix and drink formulation is an oral suspension of AZD6244 as the free-base for dispersion in an aqueous solution of sulphobutylether β-cyclodextrin (Captisol®).

**Target patient population and sample size**

This study recruited patients aged at least 18 years, with advanced NSCLC, who had failed 1 or 2 prior chemotherapeutic regimens, with a World Health Organisation performance score of 0 to 2 and life expectancy of more than 12 weeks. Patients who had received prior therapy with a mitogen activated protein kinase kinase inhibitor or pemetrexed, or who had brain metastases or spinal cord compression (unless treated and stable off steroids for 1 month) were not eligible.

The primary outcome variable was a progression event defined as the earliest of:

- Objective and/or clinical disease progression (as measured using Response Evaluation Criteria in Solid Tumours) on or before the data cut-off point, or
- Death from any cause

A total of 38 progression events would ensure the study had at least 80% power to detect a true hazard ratio (HR) of 0.50 at the 2-sided 20% significance level. Therefore, a result from this Phase II study was considered to be statistically significant if the 2-sided p value was less than 0.2. No events beyond the mandatory tumour assessment visit (MTAV; 11 July±3 days) were used in data analyses. The date of data cut-off for this study was 14 July 2007.

**Duration of treatment**

Patients received investigational product (IP; AZD6244 100 mg BD or pemetrexed 500 mg/$m^2$ over 10 minutes every 3 weeks) 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.

**Patient population**

A total of 84 patients were randomised to the study from 10 centres in 3 countries (US, Bulgaria and Romania); 40 patients were assigned to the AZD6244 group and 44 patients assigned to the pemetrexed group. In total, 29 (73 %) patients in the AZD6244 group and 26 (59%) patients in the pemetrexed group had discontinued IP on or before the MTAV, primarily because the condition under investigation worsened (disease progression). A total of 26 (31%) patients were still receiving IP at the MTAV.

The 2 treatment groups were generally comparable for demographic and baseline characteristics. The majority of patients were male in both treatment groups. The mean (and median) ages of patients in both treatment groups were: 59.2 (61.5) years in the AZD6244 group and 62.7 (63.5) years in the pemetrexed treatment group. The majority of patients (>95%) in each group were Caucasian, reflecting the countries that were participating in the study. Most patients in both treatment groups had received 1 prior therapy for NSCLC (78% of patients in the AZD6244 group and 80% of patients in the pemetrexed group). The population was considered to be representative of the broader population of patients with advanced NSCLC.

**Summary of efficacy results**

In the intent-to-treat (ITT) analysis set, 28 (70%) patients in the AZD6244 group compared with 26 (59%) patients in the pemetrexed group had a disease progression event. The resulting HR was 1.35 (2-sided 80% confidence interval [CI]: 0.93, 1.94; 2-sided 95% CI: 0.77, 2.36; p=0.30) indicating a lower risk of disease progression in the pemetrexed group; however, this difference was not statistically significant at the pre-defined significance level of p<0.2 (Table S1).

**Table S1 Hazard ratio between treatment groups of the number of patients with at least 1 disease progression event: ITT analysis set**

| Randomised Treatment | n | Number of Patients with an Event (%)[a] | Comparison Between Groups | | | |
|---|---|---|---|---|---|---|
| | | | Hazard Ratio[b,c] | 2-sided 80% CI | 2-sided 95% CI | 2-sided p-value |
| 100 mg AZD6244 | 40 | 28 (70) | 1.35 | 0.93, 1.94 | 0.77, 2.36 | 0.30 |
| 500 mg/m$^2$ pemetrexed | 44 | 26 (59) | | | | |

[a] Three patients (2 patients in the AZD6244 group; 1 patient in the pemetrexed group) had no evidence of disease progression but were not scanned within the window for the mandatory tumour assessment visit (11 July±3 days).
[b] Analysed using a logistic regression model with a complementary log-log link with a factor for treatment group.
[c] Values less than 1 imply a lower risk of disease progression with AZD6244.

In the evaluable for safety (EFS) analysis set, 27 (68%) patients in the AZD6244 group had a disease progression event compared with 25 (61%) patients pemetrexed group, resulting in a HR of 1.19 (2-sided 80% CI: 0.82, 1.73; 2-sided 95% CI: 0.68, 2.11; p=0.54); however, this difference was not statistically significant.

There was no difference between the 2 treatment groups in progression free survival (PFS) in the ITT analysis set (HR: 1.08; 2-sided 80% CI: 0.75, 1.54; 2-sided 95% CI: 0.62, 1.86; p=0.79). There was also no difference between the 2 treatment groups in PFS in the EFS analysis set (HR: 0.97; 2-sided 80% CI: 0.67, 1.39; 2-sided 95% CI: 0.55, 1.69; p=0.90).

Similar results were observed when the analyses were adjusted for the number of prior therapies or tumour cell type.

In total, at the time of the MTAV, 4 patients in the ITT analysis set and the EFS analysis set had achieved a best overall response of complete response (1 patient in the pemetrexed group) or partial response (2 patients in the AZD6244 group, 1 patient in the pemetrexed group) to treatment.

**Summary of safety results**

At the time of data cut-off, median actual exposure to AZD6244 and pemetrexed was 63 days and 61 days, respectively.

In total, 10 (25%) patients in the AZD6244 group and 8 (20%) patients in the pemetrexed group experienced AEs that led to dose reduction, dose interruption or permanent discontinuation of randomised treatment.

The number and types of AEs reported were consistent with the nature of the study treatments and the disease under study. The majority of patients in both treatment arms experienced at least 1 AE that was related to study medication. Dermatitis acneiform, diarrhoea, nausea, and vomiting were the most common AEs reported with AZD6244 therapy. These events are consistent with the previously reported safety profile for AZD6244 and primarily consisted of Common Terminology Criteria for AEs (CTCAE) Grade 1 (mild) or 2 (moderate) events. The AEs of fatigue, anaemia, nausea and anorexia that were the most commonly reported with pemetrexed are consistent with those reported previously for pemetrexed. CTCAE Grade 3 or higher AEs were experienced by 10 (25%) and 11 (27%) of patients in the AZD6244 and pemetrexed groups, respectively. More patients in the pemetrexed group experienced CTCAE Grade 4 events (5 [12%] patients; neutropenia [2 patients], hypercalcaemia, hyperglycaemia and myelodysplastic syndrome) compared with the AZD6244 group (1 [3%] patient; dyspnoea). Most CTCAE Grade 3 events occurred in a single patient only (AZD6244, 8 [20%] patients; pemetrexed, 9 [22%] patients). The most common CTCAE Grade 3 or higher events were dermatitis acneiform (4 patients [10%]) in the AZD6244 group, and neutropenia (4 patients [10%]), anaemia (2 patients [5%]), fatigue (2 patients [5%]) and leukopenia (2 patients [5%]) in the pemetrexed treatment group.

A total 16 deaths were recorded prior to study termination (with study termination defined as being 30 days after the last dose of study treatment for each individual patient). There were 8 deaths in each treatment group, the majority of which were related to disease progression (two patients in each treatment group had an AE with an outcome of death). Overall, 11 (14%) patients reported at least 1 SAE during treatment or within the 30-day period of the end of treatment; 4 (10%) patients in the AZD6244 group and 7 (17%) patients in the pemetrexed group. The only SAE to be reported by more than 1 patient in either treatment group was neutropenia (2 [5%] patients in the pemetrexed treatment group; 1 patient had 2 SAEs of neutropenia). The number and type of SAEs in both treatment groups were indicative of a population with advanced NSCLC.

No clinically significant changes in laboratory parameters were observed as a consequence of dosing with AZD6244 in this study.

For patients that continued to receive AZD6244 after the data cut-off, only SAE data will be collected. This data is not included in this report, but will be reported to Regulatory Authorities in accordance with standard pharmacovigilance procedures.