Drug Substance(s)	ZD6474	**SYNOPSIS**	(For national authority use only)
Study Code	D4200C00041		
Date	08 November 2006		

A Phase I, Open-Label Study to Assess the Safety and Tolerability of ZD6474 in Combination with Pemetrexed (Alimta™) in Patients with Locally-Advanced or Metastatic Non-Small Cell Lung Cancer after Failure of Prior Chemotherapy

Study centre(s)

Up to 30 patients with histologically- or cytologically-confirmed locally-advanced or metastatic non-small cell lung cancer (NSCLC), stage III or IV, who had progressed on first-line therapy, had measurable disease and were eligible for second-line therapy with pemetrexed and ZD6474, were planned to be recruited from approximately 6 centres in Australia, Belgium and Germany. The final number enrolled was 24, and these patients were recruited across 5 centres.

Study dates		Phase of development
First patient enrolled	20 July 2005	Clinical Pharmacology (I)
Last patient completed	N/A (addendum report to follow)	
Data cut-off date	24 May 2006	

End of study was defined as the date the last patient ceases treatment with ZD6474 and completes all associated follow up assessments.

Objectives

The primary objective of the study was to establish the safety and tolerability of AstraZeneca ZD6474 when administered in combination with pemetrexed (Alimta™) to patients with locally-advanced or metastatic NSCLC after failure of prior chemotherapy, by assessment of adverse events (AEs), vital signs, clinical chemistry, haematology, urinalysis, electrocardiogram (ECG) and physical examination.

The secondary objectives of the study were:

1. To investigate the pharmacokinetics of ZD6474 and pemetrexed when given in combination to patients with locally-advanced or metastatic NSCLC, after failure of prior chemotherapy, by assessment of appropriate pharmacokinetic (PK) parameters.

2. To make a preliminary assessment of the efficacy of ZD6474 and pemetrexed when given in combination to patients with locally-advanced or metastatic NSCLC, after failure of prior chemotherapy, as measured by an objective response rate based on Response Evaluation Criteria in Solid Tumours (RECIST).

The exploratory objectives of the study were:

1. To obtain archival tumour samples for Deoxyribonucleic acid (DNA) extraction and mutational analysis of the Epidermal Growth Factor Receptor (EGFR) gene and other relevant genes.

2. To obtain blood samples for DNA extraction for future pharmacogenetic analysis of potential correlative markers of the activity of ZD6474 and drugs taken in combination with ZD6474 (ie, pemetrexed).

Study design

This was a Phase I, multi-centre, open-label, ascending-dose study to establish the safety and tolerability of once daily oral doses of ZD6474 when administered with standard 21-day treatment cycles of pemetrexed to up to 30 patients with locally-advanced or metastatic NSCLC after failure of prior chemotherapy.

An initial cohort of up to 10 patients was to receive 100 mg ZD6474. Following safety review of these patients, if less than 2 patients experienced dose-limiting toxicity (DLT) related to ZD6474, a second cohort of up to 10 patients was to receive 300 mg ZD6474. If 300 mg was not tolerated, an intermediate dose of 200 mg could be investigated in up to 10 additional patients.

During the study, only 1 patient experienced a DLT in the 100 mg cohort, so a second cohort then received 300 mg ZD6474. Only 1 patient experienced a DLT in the 300-mg cohort, so a third cohort was not required to investigate a 200-mg dose.

Target patient population and sample size

Up to 30 patients with histologically- or cytologically-confirmed locally-advanced or metastatic NSCLC (stage III or IV), who had progressed on first-line therapy, had measurable disease, and were eligible for second-line therapy with pemetrexed and ZD6474 were to be enrolled in the study.

In total, 24 patients were enrolled in the study, but 3 of these were screening failures, so 21 patients received study medication (10 patients in the 100-mg ZD6474 cohort, and 11 patients in 300-mg cohort). Six patients per cohort were required to be evaluable for safety; evaluable patients were to have been dosed with ZD6474 and pemetrexed for at least 6 weeks (ie, they were to have received at least 3 doses of pemetrexed, in combination with daily doses of ZD6474, and were to have had the associated safety assessments), or were to have experienced a DLT prior to completion of this dosing regimen.

Seven patients who received 100 mg ZD6474 treatment were evaluable for safety at data cut-off. Six patients who received 300 mg ZD6474 treatment were evaluable for safety at data cut-off.

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

Once-daily oral dose of ZD6474 (100 mg or 300 mg) in combination with standard 21-day treatment cycles of pemetrexed (sourced locally) administered at a dose 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The following batches of ZD6474 were used in this study: P/4021/22 (50 mg), P/4136/05 (50 mg), P/4136/06 (100 mg), P/4604/41 (100 mg), P/4604/29 (300 mg).

Duration of treatment

ZD6474 was to be taken for at least 6 weeks (in combination with at least 3 doses of pemetrexed). After this period, patients could continue daily oral dosing of ZD6474 in combination with pemetrexed, or could remain on ZD6474 alone, assuming they did not meet a withdrawal criterion, (including disease progression), were free from intolerable toxicity, and, in the investigator's opinion, were receiving some benefit from the therapy.

Variables

- **Safety**

  The safety variables were the primary outcome variables for the study:
  AEs, haematology, clinical chemistry, urinalysis, ECG, vital signs, physical examination

- **Pharmacokinetic**

  – **ZD6474**:
  Pre-dose plasma concentrations
  Maximum (peak) steady state drug concentration in plasma during dosing interval ($C_{ss,max}$)
  Minimum steady state drug concentration in plasma during dosing interval ($C_{ss,min}$)
  Time to reach peak or maximum concentration or maximum response following drug administration (t_{max})
  Area under the plasma concentration-time curve during any dosing interval at steady state (AUC_{ss})
  Total body clearance of drug from plasma after oral dosing (CL/F)

  – **Pemetrexed**:
  Maximum plasma (peak) drug concentration after single dose administration (C_{max})
  Area under plasma concentration-time curve from zero to infinity (AUC)
  Terminal half-life ($t_{1/2}$)
  Volume of distribution (apparent) at steady state (V_{ss})
  Time to reach peak or maximum concentration following drug administration (t_{max})
  Total body clearance of drug from plasma (CL)

- **Efficacy**

  Objective response rate (ORR) of the tumour, based on RECIST

- **Pharmacogenetics**

  Optional samples for retrospective genotyping

Statistical methods

There was to be no formal statistical analysis of the safety data. All data were to be listed and summarised.

There was to be no formal statistical analysis for a PK interaction between ZD6474 and pemetrexed. This was to be assessed by comparison of the summary statistics for the derived PK variables of ZD6474 and pemetrexed alone and when given in combination, and by comparison of the intra-patient measures of exposure.

There was to be no formal statistical analysis of the objective tumour response rate. These data were to be listed and summarised.

There was to be no formal statistical analysis of the pharmacogenetic data. The results of any genotyping that was performed was not to form part of the Clinical Study Report (CSR).

Patient population

In total, 21 patients were dosed in this study. All patients were Caucasian. In the 100-mg cohort, there were 8 male and 2 female patients. The mean age was 61 years (range: 45 to 77 years), the mean weight was 72.6 kg (range: 47 to 120 kg), and mean BMI 24.9 kg/m^2 (range: 18 to 40 kg/m^2). In the 300-mg cohort, there were 6 male and 5 female patients. The mean age was 60 years (range 44 to 73 years), the mean weight was 80.7 kg [range: 53 to 132 kg], and mean BMI 28.7 kg/m^2 (range: 19 to 46 kg/m^2). The demographic characteristics of the patients in this study were mainly well balanced between the 2 cohorts. There was a slight difference in the sex distribution between the 2 cohorts, but this was not anticipated to affect the safety and tolerability results of the study.

Ten patients received once-daily oral doses of ZD6474 100 mg in combination with standard 21-day treatment cycles of pemetrexed. Less than 2 patients experienced dose-limiting toxicity (DLT) that was considered to be possibly related to ZD6474, so a second cohort of 11 patients were enrolled and received once-daily oral doses of ZD6474 300 mg in combination with standard 21-day treatment cycles of pemetrexed. Less than 2 patients experienced DLT in the 300-mg cohort, so a third cohort to investigate a 200-mg dose was not required.

Twenty-one patients received study medication (10 patients in the 100-mg ZD6474 cohort, and 11 patients in 300-mg cohort). Six patients per cohort were required to be evaluable for safety; evaluable patients were to have been dosed with ZD6474 and pemetrexed for at least 6 weeks (ie, they were to have received at least 3 doses of pemetrexed, in combination with daily doses of ZD6474, and were to have had the associated safety assessments), or were to have experienced a DLT prior to completion of this dosing regimen.

Table S1 gives a summary of patient status at the time of data cut-off (24 May 2006).

Table S1 Summary of patient status at data cut-off

Patient status at data cut-off [a]	Number of patients (%)		
	100 mg cohort (n=10)	300 mg cohort (n=11)	Total (n=21)
Evaluable for safety [b] at data cut-off	7 (70.0)	6 (54.5)	13 (61.9)
Evaluable for PK at data cut-off	6 (60.0)	4 (36.4) [c]	10 (47.6) [c]
Completed 60-day safety follow-up at data cut-off [d]	9 (90.0)	6 (54.5)	15 (71.4)
Ongoing in study at data cut-off	1 (10.0)	5 (45.5)	6 (28.6)
Ongoing on ZD6474 alone	0 (0.0)	0 (0.0)	0 (0.0)
Ongoing on combination treatment	0 (0.0)	3 (27.3)	3 (14.3)
Ongoing for follow-up [e]	1 (10.0)	2 (18.2)	3 (14.3)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)

[a] Note that rows are not mutually exclusive (eg, patient may be ongoing on ZD6474 but may also have been evaluable for safety/PK at data cut-off)

[b] A patient who was evaluable for safety was defined as having received at least 6 weeks of combination treatment (ie, treated up to at least Day 2 of Cycle 3 of pemetrexed, with associated safety measurements collected), or having experienced a DLT prior to this. One evaluable patient in each cohort experienced a DLT.

[c] This figure includes one patient (Patient 43 Centre 5, E0005997) who was evaluable for ZD6474 PK but not evaluable for pemetrexed PK.

[d] This category includes patients who have died during treatment.

[e] Patients off all treatment or ongoing on pemetrexed, and ongoing for safety and efficacy follow-up

At data cut-off, 1 patient continued in the 100-mg cohort (ongoing for safety and efficacy follow-up) and 5 patients in the 300-mg cohort (3 receiving combination treatment, and 2 ongoing for safety and efficacy follow-up [and still receiving pemetrexed treatment]). Safety and efficacy data for patients ongoing in the study after data cut-off will be collected and reported in an addendum report.

Table S2 gives a summary of patients who discontinued the study before data cut-off.

Table S2 Summary of patient who discontinued study before data cut-off

Patient status at data cut-off [a]	Number of patients (%)		
	100 mg cohort (n=10)	300 mg cohort (n=11)	Total (n=21)
Patients ongoing study at data cut-off	1 (10.0)	5 (45.5)	6 (28.6)
Patients who discontinued the study [b]	9 (90.0)	6 (54.5)	15 (71.4)
Adverse event	0 (0.0)	1 (9.1)	1 (4.8)
Disease progression [c]	5 (50.0)	1 (9.1)	6 (28.6)
Patient not willing to continue in study	1 (10.0)	0 (0.0)	1 (4.8)
Other	3 (30.0)	4 (36.4)	7 (33.3)
Patients who discontinued ZD6474 prior to data cut-off	10 (100.0)	8 (72.7)	18 (85.7)
Adverse event	1 (10.0)	3 (27.3)	4 (19.1)
Disease progression	7 (70.0)	3 (27.3)	10 (47.6)
Patient not willing to continue treatment	1 (10.0)	0 (0.0)	1 (4.8)
Other [d]	1 (10.0)	2 (18.2)	3 (14.3)
Patients who discontinued pemetrexed prior to data cut-off	10 (100.0)	6 (54.5)	16 (76.2)
Adverse event	2 (20.0)	1 (9.1)	3 (14.3)
Disease progression	6 (60.0)	3 (27.3)	9 (42.9)
Patient not willing to continue treatment	1 (10.0)	0 (0.0)	1 (4.8)
Other [d]	1 (10.0)	2 (18.2)	3 (14.3)

[a] Note that rows are not mutually exclusive
[b] This category includes all evaluable and non-evaluable patients who had completed follow-up prior to data cut-off
[c] Disease progression was listed as 'Condition under investigation worsened' in the CRF for patients who discontinued the study.
[d] Reasons classed under this category were "progressive disease", "death", and "death due to disease progression".

Data from all 21 dosed patients were included in the data listings. Data from all 21 patients who received at least one dose of ZD6474 were included in the safety summary. These patients also provided the efficacy data. All 10 patients with valid PK data were included in the PK summary. All 10 patients were included in the summary of adverse events for ZD6474 100 mg dose. All 11 patients were included in the summary of adverse events for ZD6474 300 mg dose.

Summary of safety results

Both 100 mg and 300 mg ZD6474 had an acceptable tolerability profile when given in combination with pemetrexed. ZD6474 in combination with pemetrexed appeared to be

tolerated better by patients in the 100-mg cohort compared to patients in the 300-mg cohort, with a lower number of early withdrawals due to AEs seen in patients receiving 100 mg ZD6474. In the 100-mg cohort, 8 (80.0%) patients received 3 or more cycles of combined study treatment, compared to 5 (45.5%) patients in the 300-mg cohort. Moreover, 4 patients (36.4%) in the 300-mg cohort discontinued study treatment during the first chemotherapy cycle.

One DLT was recorded in each cohort. In the 100-mg cohort, there was a DLT of prolonged QTc interval (>100 ms increase from baseline, but absolute QTc of <500 ms), and in the 300-mg cohort, there was a DLT of Interstitial Lung Disease (ILD). As only 1 out of the 6 patients who were evaluable for safety in each cohort experienced a DLT, the protocol definition of a tolerable dose was met in both cohorts.

All 21 patients included in this study experienced one or more AEs. A total of 20 (95.2%) patients experienced an AE that was considered by the investigator or AstraZeneca physician to be related to ZD6474 (10 patients in each cohort). The most frequently reported AEs were rash (10 [47.6%] patients), anorexia (10 [47.6%] patients), fatigue (10 [47.6%] patients), and diarrhoea (10 [47.6%] patients). The most commonly reported ZD6474-related AEs were rash (7 [33.3%] patients), anorexia (7 [33.3%] patients), fatigue (7 [33.3%] patients), and diarrhoea (4 [19.0%] patients). ZD6474-related AEs seen in this study were consistent with the expected safety profile of ZD6474.

CTCAE grade 2 or higher increase in LFTs was observed in 12 (57.1%) patients (6 patients in the 100-mg cohort and 6 in the 300-mg cohort). Only 4 (19.0%) patients had clinically-significant increases in LFTs that were reported as AEs (3 patients on 100 mg and 1 on 300 mg), and these AEs were considered to be related to ZD6474 (and pemetrexed) in only 3 (14.3%) patients.

The most commonly-experienced CTCAE grade 3 or 4 AEs were: increased gamma-glutamyltransferase (GGT) (4 [19.0%] patients), anorexia (3 [14.3%] patients), dyspnoea (3 [14.3%] patients), anaemia (2 [9.5%] patients), hyponatraemia (2 [9.5%] patients), febrile neutropenia (2 [9.5%] patients), and lymphopenia (2 [9.5%] patients).

Three patients were reported to have died as a result of an AE. The AEs associated with the deaths were bronchopneumonia (100-mg cohort), pneumonia (300-mg cohort) and cardiomegaly (300-mg cohort). None of these deaths were considered by the investigator to be causally-related to ZD6474.

A total of 13 patients (61.9%) had at least 1 SAE during the study. Thirteen SAEs occurred in 8 (80.0%) patients in the 100-mg cohort (2 of these SAEs were assessed as being causally related), and 8 SAEs occurred in 5 (45.5%) patients in the 300-mg cohort (1 causally related).

A total of 7 (33.3%) patients experienced an AE leading to discontinuation of ZD6474. Two (20%) patients in the 100-mg cohort and 5 (45.5%) in the 300-mg cohort experienced a broad range of AEs which led to discontinuation of ZD6474. Four of these AEs were

considered to be related to ZD6474: pulmonary microemboli, nausea and fatigue (both in 1 patient), and pneumonitis (interstitial lung disease).

Eleven (52.4%) patients experienced other significant AEs (OAEs): 7 (70.0%) patients in the 100-mg cohort, 4 (36.4%) patients in the 300-mg cohort. Two (18.2%) of these 11 patients (both in the 300-mg cohort) had an AE leading to a ZD6474 dose change, 9 (81.8%) of these 11 had an AE leading to ZD6474 being temporarily stopped, and 8 (72.7%) of these 11 had an AE which was assessed by the sponsor as being a significant AE. There were 29 OAEs in total: 22 in the 100-mg cohort, 7 in the 300-mg cohort.

Due to the small number of patients in this study and the longer mean actual exposure at ZD6474 100 mg (94.2 days) compared to 300 mg (44.7 days), it would not be reliable to assess any dose-related difference in the number of AEs between cohorts.

Other than increased LFTs, there were no unexpected laboratory findings in this study.

Regarding ECG observations, 1 (4.8%) patient experienced QTc interval prolongation in the 100-mg cohort, meeting 1 of the protocol-defined criteria for QTc prolongation (a single increase >100 ms from baseline). Hypertension was experienced by only 1 (4.8%) patient in the 300-mg cohort and none in the 100-mg cohort. There were no clinically-significant findings for patients' vital signs.

Summary of pharmacokinetic results

For both dose levels of ZD6474, the gmean AUC_{ss}, in the presence of pemetrexed, was comparable to that when given alone (15410 ng.h/mL compared to 14810 ng.h/mL for 100 mg, and 23620 ng.h/mL compared to 20460 ng.h/mL for 300 mg), with similar inter-patient variability (%CVs). The gmean ratios of AUC_{ss} were both near to 1.0, at 1.041 and 1.155 for each group, respectively. Parallel results were observed for the gmean and the gmean ratios of $C_{ss, max}$.

For both dose levels of ZD6474, the gmean AUC of pemetrexed, in the presence of ZD6474, was comparable to that when given alone (313.2 ng.h/mL compared to 278.6 ng.h/mL for 100 mg, and 258.8 ng.h/mL compared to 250.5 ng.h/mL for 300 mg) although the inter-patient variability was slightly greater when in the presence of ZD6474. The gmean ratios of AUC were both near to 1.0, at 1.124 and 1.033 for each group, respectively. Parallel results were observed for the gmean and the gmean ratios of C_{max}.

Summary of efficacy results

Preliminary assessment of the efficacy of ZD6474 and pemetrexed when given in combination, based on RECIST assessments of objective response rate, showed no clear dose response for ZD6474 (100 mg and 300 mg). One confirmed partial response (PR) was observed (in a female patient in the 100-mg cohort). Thirteen patients had stable disease (SD) ≥6 weeks (7 in the 100-mg cohort, 6 in the 300-mg cohort). There were 6 (60.0%) RECIST progressions in the 100-mg cohort, 3 (27.3%) in the 300-mg cohort. There were 3 (30.0%) deaths in the absence of progression in the 100-mg cohort, 2 (18.2%) in the 300-mg cohort.

The median time to progression (including death in the absence of objective disease progression) was 111 days in the 100-mg cohort and 117 days in the 300-mg cohort.