AstraZeneca

Drug product:		**SYNOPSIS**	
Drug substance(s):	ZD6474		
Edition No.:	Final		
Study code:	D4200C00003		
Date:	5 November 2006		

A Phase II, Randomized, Double-blind, 2-Part, Multicenter Study To Compare the Efficacy of ZD6474 with the Efficacy of ZD1839 (Iressa™) in Patients With Locally Advanced or Metastatic (IIIB/IV) Non-small Cell Lung Cancer after Failure of either First-Line and/or Second-line Platinum-based Chemotherapy and to Assess the Activity of ZD6474 in Patients Following Failure of Treatment With ZD1839

Study center(s)

This study was conducted in 37 centers in 6 countries (Argentina [5], Belgium [5], Germany [3], South Africa [8], UK [5], and US [11]).

Publications

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Study dates		**Phase of development**
First patient enrolled	22 May 2003	Therapeutic exploratory (II)
Last patient completed	1 patient still receiving active drug as of 31 Oct 2006.	

Objectives

The study was conducted in 2 parts. In Part A patients were randomized to 1 of 2 double-blind treatment arms (300 mg ZD6474 or 250 mg ZD1839). Upon progression or toxicities in Part A, patients had the option to enter Part B of the study. In Part B patients received the alternate study treatment to that given in Part A. The primary and secondary objectives of the respective parts of the study are listed below; the pharmacokinetic (PK) and pharmacokinetic-

pharmacodynamic (PK-PD) objectives (incorporating data from both parts of the study) are listed following those for Part A and B.

PART A

The primary objectives of Part A were the following:

- To compare time to progression (PFS) for patients with non-small cell lung cancer (NSCLC) treated with ZD6474 with that for patients treated with ZD1839
- To assess the tolerability and safety of ZD6474 and ZD1839

The secondary objectives of Part A were the following:

- To compare the objective response for patients with NSCLC treated with ZD6474 with that for patients treated with ZD1839 using modified RECIST (Appendix F of the protocol in Appendix 12.1.1 of this report)
- To compare the disease control at 8 weeks (defined as stable disease or better) for patients treated with ZD6474 with that for patients treated with ZD1839
- To compare tumor-related symptoms of patients given either ZD6474 or ZD1839 by assessment of the quality of life (QOL) and the lung cancer subscale (LCS) from the Functional Assessment of Cancer Therapy - Lung Cancer (FACT-L) questionnaire
- To assess the performance status of patients given either ZD6474 or ZD1839 using World Health Organization (WHO) performance status
- To compare the survival of patients randomized to initial treatment with either ZD6474 or ZD1839. **Note:** this objective used data from Part A and Part B of the study. It was planned that patients were given the initial randomized treatment followed by the alternate treatment.

The exploratory objectives of Part A were the following:

- To explore the biological effects of ZD6474 and ZD1839 on tumor perfusion and metabolic activity determined by positron emission tomography using a ^{15}O radionuclide isotope of oxygen ($H_2{}^{15}O$ PET) and 2-[F-18] Fluoro-2-deoxy-D-glucose-positron emission tomography (FDG PET) respectively, and to investigate the relationship between the biological assessments and objective tumor response, PFS and exposure in selected centers in Part A.
- To explore the biological effect of ZD6474 on plasma VEGF and to investigate whether baseline plasma VEGF level has any prognostic significance

PART B

Following withdrawal from the study treatment because of toxicity or progression of disease in Part A, patients had the option to enter Part B where they were given the alternate treatment to that given in Part A.

The primary objectives of Part B were the following:

- To assess the PFS for patients with NSCLC given ZD6474 or ZD1839 following treatment with the alternate study therapy in Part A
- To assess the tolerability and safety of ZD6474 and ZD1839

The secondary objectives of Part B were the following:

- To assess the objective response for patients with NSCLC given ZD6474 or ZD1839 following treatment with the alternate study therapy in Part A using RECIST
- To assess the disease control at 8 weeks for patients given ZD6474 or ZD1839 following treatment with the alternate study therapy in Part A
- To assess tumor-related symptoms of patients given ZD6474 or ZD1839 following treatment with the alternate study therapy in Part A by assessment of QOL and LCS from the FACT-L questionnaire
- To assess the performance status of patients given ZD6474 or ZD1839 following treatment with the alternate study therapy in Part A using WHO performance status

The exploratory objectives of Part B were the following:

- To explore the biological effect of ZD6474 on plasma VEGF and to investigate whether baseline plasma VEGF level has any prognostic significance

Pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PK-PD) objectives:

The secondary PK objectives (combining data from Part A and B) were the following:

- Characterize the population PK of ZD6474 in patients with NSCLC given either alone or in patients following treatment with ZD1839 who subsequently received ZD6474 for a minimum of 28 days, taking into account demographic and clinical covariates to describe the variability observed
- Characterize the population PK of ZD1839 in patients with NSCLC given either alone or in patients following treatment with ZD6474 who subsequently received ZD1839 for a minimum of 28 days, taking into account demographic and clinical covariates to describe the variability observed

The secondary PK-PD objectives combining data from Part A and B were the following:

- Characterize the PK-PD relationship, if any, between ZD6474 exposure and electrocardiogram (ECG) measurements, adverse events, objective response rates, and PFS

- Characterize the PK-PD relationship, if any, between ZD1839 exposure and ECG measurements, adverse events, objective response rates, and PFS

Study design

This was a phase II, randomized, double-blind, 2-part, multicenter study conducted in 168 patients with locally advanced or metastatic (IIIB/IV) NSCLC after failure of either first-line and/or second-line platinum-based chemotherapy.

Target patient population

Male and female patients at least 18 years of age with prior histologic or cytologic confirmation of locally advanced or metastatic (IIIB/IV) NSCLC who had failure of either first-line and/or second-line chemotherapy, either of which was platinum-based (the prior regimen must have failed the patient because of toxicity or progression of tumor).

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

In order to maintain the study blind, each patient received 2 tablets, one of which was placebo. The study blind was maintained, even in the event of a dose reduction.

Investigational Product:

ZD6474 50 mg, 100 mg (or matching placebo), 300 mg (or matching placebo) given orally, once daily in tablet form.

Comparator:

ZD1839 (250 mg) or matching placebo given orally, once daily in tablet form.

Duration of treatment

Both ZD6474 and ZD1839 were taken on a daily basis until disease progression or until other withdrawal criteria were met. Patients could continue treatment in Part A as long as they were benefiting from treatment, there was no evidence of tumor progression, and they met no other withdrawal criteria. Following study treatment withdrawal because of toxicity or disease progression and a washout period of 4 weeks, the patient was then eligible to be given the alternate treatment in Part B. Once patients had entered Part B of the study, they received study treatment until disease progression or other withdrawal criteria were met. A longer washout period was acceptable on discussion between the Investigator and AstraZeneca. Patients who had a QTc prolongation or Interstitial Lung disease in Part A were not permitted to enter Part B.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

Part A:

- Primary variable: PFS (In the absence of progression, death was counted as a progression event only if it occurred within 3 months of the last evaluable RECIST assessment)

- Secondary variables: Objective response; disease control (defined as stable disease or better) at 8 weeks; time to death [Note: this outcome variable used data from Part A and B of the study]; and World Health Organization (WHO) performance status

- Exploratory outcome variables: For selected centers, glucose metabolic rate (MRglc), and Standard Uptake Value (SUV) from FDG PET, and perfusion from $H_2{}^{15}O$ PET at the Day 23-28 assessments of Cycle 1 and Cycle 2; for selected centers, investigation of the relationship between objective response, PFS and exposure and PET endpoints [MRglc, SUV, and $H_2{}^{15}O$ perfusion] from all PET assessments; plasma VEGF level;

Patient reported outcomes (PROs):

- Secondary outcome variable: QOL and LCS from the FACT-L questionnaire

Safety

- Primary variable: -Incidence, Common Toxicity Criteria (CTC) grade, and type of adverse events (AEs), clinically significant laboratory abnormalities or changes in vital signs, and ECG changes

PART B

Efficacy

- Primary outcome variable: PFS (In the absence of progression, death was counted as a progression event only if it occurred within 3 months of the last evaluable RECIST assessment) in patients following treatment with the alternate study treatment (calculated from the start of treatment in Part B)

- Secondary outcome variables: Objective response in patients following treatment with the alternate study treatment; disease control (defined as stable disease or better) at 8 weeks in patients following treatment with the alternate study treatment; and WHO performance status in patients following treatment with the alternate study treatment

- Exploratory outcome variables: Plasma VEGF level

Patient reported outcomes (PROs)

- Secondary outcome variable: QOL and LCS from the FACT-L questionnaire in patients following treatment with the alternate study treatment

Safety

- Primary outcome variable: Incidence, CTC grade, and type of AEs, clinically significant laboratory abnormalities or changes in vital signs, and ECG changes

Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Analysis: PART A and B

Pharmacokinetic

- Secondary outcome variables:

  - Total body clearance of drug at steady state (CLss/f) and volume of distribution at steady state (Vss/f) of ZD6474 following administration of multiple oral doses, with associated inter-patient variabilities. Individual empirical Bayesian derived maximum concentration (C_{max}), area under the curve at steady state (AUC_{ss}) and minimum concentration (C_{min}) values.

  - CLss/f and Vss/f of ZD1839 following administration of multiple oral doses, with associated inter-patient variabilities. Individual empirical Bayesian derived C_{max}, AUC_{ss} and C_{min} values.

Pharmacokinetic-Pharmacodynamic (PK-PD)

- Secondary outcome variables:

  - Probability of QTc prolongation and of the concentration of ZD6474 associated with risk. Probability of adverse events, objective response rates, and PFS and determination if AUC_{ss}, C_{max}, C_{min} were the most significant predictors of events.

  - Probability of QTc prolongation and of the concentration of ZD1839 associated with risk. Probability of adverse events, objective response rates, and PFS and determination if AUC_{ss}, C_{max}, C_{min} are the most significant predictors of events

Statistical methods

The primary efficacy objective of Part A was to compare the PFS of ZD6474 and ZD1839. If data were analyzed when 120 progression events had occurred, and if the true hazard ratio (ZD6474:ZD1839) for PFS was 0.75 (which if data were exponentially distributed would correspond to a 33% delay in median PFS with ZD6474), there was a greater than 75% probability of observing a one-sided hypothesis test that resulted in the corresponding test statistic having a p-value less than 0.2.

An initial interim analysis of Part A data was performed before the end of the study. Although this is described as an interim analysis, it was intended that this would be the primary analysis of data from Part A of the study. The purpose was not an interim as such, but was in order to provide answers to questions from Part A of the study, without having to wait for Part B to be completed. The timing of the analysis was therefore based upon the required number of events specified in the sample size calculations for the study to meet the objectives of Part A (ie, 120 progression events). At the end of the study, all data from both Part A and Part B were included in the analysis for the final clinical study report.

Efficacy data from Part A and Part B were summarized separately. Data were summarized on an intention-to-treat (ITT) basis, using randomized treatment. Note: time to death used data collected in Part A and Part B of the study. Formal statistical comparisons were only performed on data from Part A of the study. Data from Part B of the study was summarized using descriptive statistics only.

For Part A, PFS and time to death was analyzed using a Cox proportional hazards regression model. The model allowed for the effect of treatment and included terms for sex, histology (adenocarcinoma versus other types) and previous response to therapy. Objective response rate and disease control rate at 8 weeks were analyzed using logistic regression and using the same set of covariates.

In Part B, response and progression were calculated in comparison to the baseline tumor measurements obtained before starting treatment in Part B.

Safety data were presented for Part A and Part B separately, and also presented in a combined summary according to treatment received in each study part.

Patient population

A total of 168 patients were randomized to treatment in this study; 83 patients were initially randomized to receive ZD6474 and 85 were randomized to receive ZD1839. No patients were excluded from the analysis based on deviations as an intention-to-treat (ITT) approach was adopted for all analyses. The majority of deviations were related to inclusion and exclusion criteria and deviations in sampling times of assessment such as PK, laboratory and ECG assessments.

Overall, the treatment groups were well-balanced in terms of demographic and baseline characteristics. Most patients had a tumor histology of adenocarcinoma, stage IV disease, and were ex-smokers. The estimated treatment compliance in both treatment groups was >90%.

Some patients in both groups received disallowed concomitant medications (medications that could prolong QTc interval), but they were not censored and their data were used in the analysis of the trial. However, there was no evidence to suggest that these patients had any difference in the incidence of QTc prolongation.

Table S1 Patient population and disposition

		Randomized Treatment		
		ZD6474 300 mg/day	**ZD1839 250 mg/day**	**All**
		(N=83)	**(N=85)**	**(N=168)**
Age (Years)	N	83	85	168
	Mean	61.8	59.8	60.8
	SD	9.22	10.69	10.01
	Median	63	61	62
	Minimum	31	32	31
	Maximum	80	78	80
Age Category	<65	48 (57.8%)	56 (65.9%)	104 (61.9%)
	≥65	35 (42.2%)	29 (34.1%)	64 (38.1%)
Sex	Male	48 (57.8%)	52 (61.2%)	100 (59.5%)
	Female	35 (42.2%)	33 (38.8%)	68 (40.5%)
Race	Caucasian	75 (90.4%)	77 (90.6%)	152 (90.5%)
	Black	3 (3.6%)	2 (2.4%)	5 (3.0%)
	Asian - Non-Japanese	2 (2.4%)	3 (3.5%)	5 (3.0%)
	Other	3 (3.6%)	3 (3.5%)	6 (3.6%)
Height (cm)	N	82	82	164
	Mean	169.4	169.8	169.6
	SD	9.21	8.74	8.95
	Median	169	170	169.5
	Minimum	144	152	144
	Maximum	189	196	196
Weight (kg)	N	83	85	168
	Mean	71	73.2	72.1
	SD	15.43	15.02	15.22
	Median	70	71.2	71
	Minimum	40.9	42.6	40.9
	Maximum	127.8	112.7	127.8

[F] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number

Efficacy and pharmacokinetic results

The primary objective of this study was to show an increase in PFS in the ZD6474 treatment arm over ZD1839 with a 1-sided nominal significance level of 0.2, as well as to assess the safety and tolerability of both drugs. This study met its primary objective and offers strong evidence of the benefit of 300 mg ZD6474 in this patient population.

The study showed that 300 mg ZD6474 significantly reduced the risk (1-sided p=0.013) of disease progression over a given period by approximately 31% compared to ZD1839 (HR= 0.69, 2 sided 95% CI: 0.50, 0.96). This translates to an approximate 45% prolongation in PFS for ZD6474 compared to ZD1839. All secondary analyses of PFS were supportive of the primary analysis. The median PFS was 11.0 weeks for ZD6474 and 8.1 weeks for ZD1839.

Objective responses were observed by 8% of patients receiving ZD6474 and 1% of patients receiving ZD1839. The odds of experiencing a response on ZD6474 were 9.8 times higher than on ZD1839 and the 1-sided p value of 0.02 was statistically significant at the nominal level of 0.2 set for this study. In this study, stable disease was categorized as "no response." However, 30 (36%) patients receiving ZD6474 and 28 (33%) patients receiving ZD1839 had stable disease for at least 8 weeks. Of these, 20 and 13 patients receiving ZD6474 and ZD1839, respectively, experienced stable disease for at least 12 weeks. The probability of being in response was generally higher for the ZD6474 arm compared to the ZD1839 arm, which is supportive of the secondary analysis of the objective response rate.

A statistically significant (1-sided p=0.066) improvement in disease control rate in patients receiving ZD6474 compared to ZD1839 was noted. No statistically significant difference in any of the QoL parameters was noted, and there was no clear distinction between the 2 treatment arms with regard to performance status.

There was no evidence of a significant advantage in overall survival for patients initially randomized to ZD6474 compared to patients initially randomized to ZD1839. Advantages in PFS did not translate to advantages in OS in this study. Safety and death data were extensively reviewed and there was no clear evidence of any systematic safety concerns leading to early deaths for patients initially randomized to ZD6474. The survival data is also confounded by the switching of therapy and the potential effect of subsequent therapies.

Safety results

This study showed that ZD6474 (300 mg) had a manageable side effect profile and that the ZD1839 safety profile was in keeping with the known safety profile of this compound. Both ZD6474 and ZD1839 were reasonably well tolerated. AEs were manageable with dose reductions and interruptions. Almost all patients in both Part A and B of the study, regardless of the drug to which they were initially randomized, experienced adverse events. However, the ZD6474 treatment arm had a higher incidence of discontinuations due to AEs and CTC

grade 3 and 4 AEs. QT prolongations (defined by the protocol) were only seen in patients who had received ZD6474 and all were asymptomatic. The most common adverse events across both treatment arms were diarrhea, fatigue, and nausea and most deaths on study were due to disease progression and not to adverse events related to ZD6474 or ZD1839. SAEs, particularly gastrointestinal disorders (ie, diarrhea); respiratory, thoracic and mediastinal disorders; and expected complications of chemotherapy or NSCLC, were observed more frequently in the 300 mg ZD6474 treatment arm. A higher incidence of adverse events in the system organ class of Infection and Infestations was observed in the ZD1839 treatment arm. AEs leading to death were also more frequent in the ZD6474 treatment arm. There were 3 and 2 patients in the ZD6474 300 mg and ZD1839 arms of the study, respectively who experienced ≥Grade 2 liver enzyme elevations. Deep venous thrombosis (DVT) was described in 1 patient in the ZD6474 arm and pulmonary embolus (PE) was described in 2 patients in the ZD6474 arm. In the ZD1839 arm, 1 patient experienced a DVT and 2 patients had subclavian vein thrombosis. No difference was seen in the vascular disorders system organ class between the 2 arms of the study. No serious hemorrhagic events were described in either arm of the study (with the exception of 1 patient receiving ZD6474 in Part B of the study who was over-anticoagulated with warfarin). Hemoptysis was described in 2 patients receiving ZD6474 and 7 patients receiving ZD1839, all cases were Grade 1. Hypertension is part of the safety profile of ZD6474 with hypertension being reported in 12% of patients. Hypertensive events were found to be manageable, with most cases of CTCAE Grade 1 or 2. Grade 3 hypertension was described in 4 patients who received ZD6474. The safety profile of both ZD6474 and ZD1839 in Part B of the study was similar to Part A with no additive toxicity after switching medications following the 4 week 'wash-out' period.

Table S2 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	**N (%) of patients who had an adverse event in each category[a]**			
	ZD6474 (300 mg) (N=83)		**ZD1839 (250 mg) (N=85)**	
Any adverse events	83	(100.0%)	84	(98.8%)
Serious adverse events	36	(43.4%)	21	(24.7%)
Serious adverse events leading to death	7	(8.4%)	3	(3.5%)
Serious adverse events not leading to death	30	(36.1%)	19	(22.4%)
Discontinuations of study treatment due to adverse events	22	(26.5%)	9	(10.6%)
Discontinuation of study treatment due to any AE	22	(26.5%)	9	(10.6%)
Any drug-related AE	67	(80.7%)	66	(77.6%)
Any CTC grade 3 or 4 AE	49	(59.0%)	35	(41.2%)
Any CTC grade 3 or 4 drug-related AE	18	(21.7%)	8	(9.4%)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Table S3 Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarized over all treatment groups (safety analysis set)

	Initial treatment received, Part A			
	ZD6474 300 mg/day (N=83)		ZD1839 250 mg/day (N=85)	
Adverse event preferred term[a]	**n**	**%**	**n**	**%**
Diarrhea	48	(57.8%)	35	(41.2%)
Fatigue	33	(39.8%)	30	(35.3%)
Nausea	23	(27.7%)	25	(29.4%)
Rash	26	(31.3%)	19	(22.4%)
Anorexia	20	(24.1%)	22	(25.9%)
Cough	19	(22.9%)	18	(21.2%)
Dyspnea	20	(24.1%)	14	(16.5%)
Constipation	18	(21.7%)	13	(15.3%)

[a] Events with a total frequency of ≥20% in either treatment group are included in this table.