SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: IRESSA™

ACTIVE INGREDIENT: ZD1839

Trial title: A Randomized, Double-blind, Parallel-group, Phase II, Multicenter Trial of Two Doses of ZD1839 (Iressa™) in Patients With Advanced NSCLC Who Have Previously Received at Least Two Chemotherapy Regimens that Contained Platinum and Docetaxel Given Concurrently or as Separate Treatment Regimens

Clinical phase: II	**First patient recruited:**	7 November 2000
	Last patient recruited:	6 April 2001
	Data cutoff:	1 August 2001
	AstraZeneca approval date:	30 November 2001

Principal investigator and location (center number):

Publications: There were no publications relative to this trial at the time of report preparation.

OBJECTIVES

Primary objectives: To evaluate objective tumor response rate and symptom improvement rate with ZD1839 at oral doses of 250 and 500 mg daily.

Secondary objectives: To estimate disease control rate, progression-free survival, overall survival, and time to worsening of symptoms; to further characterize the safety profile of ZD1839 at doses of 250 and 500 mg daily; to evaluate changes in quality of life (QOL); and to evaluate the demographic and pathophysiological factors affecting exposure to ZD1839.

Exploratory objective: To estimate correlation of epidermal growth factor receptor (EGFR) expression and probability of tumor response. (In addition, the correlation of EGFR expression and probability of symptom improvement was also planned.)

METHODS

Design: This was a randomized, parallel-group, double-blind, Phase II multicenter trial. Patients were randomly assigned to receive 250 or 500 mg of ZD1839 orally on a daily basis until disease progression or withdrawal criteria were met. The planned recruitment period was 4 months, with the trial scheduled to close 4 months after the last patient was recruited.

Population: The total number of patients expected to be exposed to trial procedures was 220. Eligible patients were those with histologically confirmed, locally advanced or metastatic non-small cell lung cancer (NSCLC) who had received prior treatment with at least 2 chemotherapy regimens that contained platinum and docetaxel given concurrently or as separate treatment regimens, and who had failed prior regimens because of disease progression within 90 days of the last dose of chemotherapy or because of unacceptable toxicity. Patients were classified at randomization by (a) World Health Organization [WHO] performance status (0 or 1 vs 2), and the number of prior treatment regimens (2 vs 3 vs 4 or more). Patients were required to be symptomatic from NSCLC as evidenced by a score of 24 points or less on the lung cancer subscale (LCS) of the functional assessment of cancer therapy-lung (FACT–L) questionnaire.

Dosage: Each dose of ZD1839 consisted of 2 tablets; the 500-mg dose consisted of two 250-mg tablets (Formulation F12653), and the 250-mg dose consisted of one 250-mg tablet and one placebo tablet (Formulation 12647). Trial treatment was administered orally once a day until disease progression or trial closure. A one-time dose reduction in ZD1839 (from 500 to 250 mg or 250 to 100 mg [Formulation F12651]) was allowed per patient if toxicity occurred.

Key assessments:

Efficacy: The primary efficacy end points were (a) objective tumor response rate (complete and partial responses), based upon the Southwest Oncology Group (SWOG)-modified UICC-WHO criteria, and (b) symptom improvement rate, from patient-reported disease-related symptoms measured by the LCS of the FACT-L questionnaire. Secondary efficacy end points included disease control rate (complete and partial responses and stable disease); progression-free survival and overall survival; time to worsening of symptoms; and patient-reported quality of life as measured by the TOI (composite of symptom, functional, and physiological domains of the FACT-L) and the total FACT-L score. To qualify as having stable disease, a patient must have had radiologic tumor assessments showing between 49% shrinkage and 49% growth compared to baseline at Days 28 and 56. An exploratory end point was EGFR expression (results of which are to be presented in a separate report).

Pharmacokinetics: Trough concentrations of ZD1839. (These data were used in a population pharmacokinetics analysis, the results of which are to be presented in a separate report.)

Safety: Safety was assessed on the basis of reported adverse events and protocol-defined toxicities of interest; laboratory test results for hematological parameters, biochemical parameters, and urinalysis; physical examinations; ophthalmologic assessments; and electrocardiographic findings.

Statistical considerations: The trial was sized to independently evaluate the 2 primary end points (objective tumor response rate and symptom improvement rate) for each ZD1839 dose. The primary analysis population for the 2 primary end points was the ITT population (patients who received at least 1 dose of trial drug, analyzed by randomized treatment). To assess

population sensitivity, these end points were also analyzed in the PP population (a subset of the ITT population that included patients who did not significantly violate or deviate from the protocol).

For each dose of ZD1839, the 1-sided significance level for each end point was calculated as the probability of the observed number or greater successes (objective responses or symptom improvements) given the sample size assuming a true event rate of 5%. If the larger of the 2 significance levels is ≤0.025, it can be concluded that the event rate for both end points is >5%. Otherwise, if the smaller of the 2 significance levels is ≤0.0125, it can be concluded that the event rate for the corresponding end point alone is >5%. With 100 patients per dose, 11 events are required to conclude that the event rate is >5% at both a 1-sided 0.025 and 0.0125 significance level (11.0% observed rate; 95% confidence interval 5.6% to 18.8%; 97.5% confidence interval 5.1% to 20.0%). A 5% rate was selected as the minimal acceptable rate for an active agent in a setting where no effective therapy is available.

The 2 doses of ZD1839 were compared with respect to the 2 primary end points with Fisher's exact test.

RESULTS

Demography: A total of 221 patients from 30 US centers were randomized in this trial, of whom 216 received ZD1839 treatment (102 assigned to 250 mg/day; 114 assigned to 500 mg/day). The first patient was randomized on 7 November 2000, and the last patient was randomized on 6 April 2001. As of the data cutoff date (1 August 2001), 39 patients were continuing in the trial.

The median age of patients who received ZD1839 treatment was 61 years (range 30 to 84 years); 56.9% were men, and 90.7% were Caucasian. The majority of patients (88.9%) had metastatic disease at trial entry. The predominant histology was adenocarcinoma (66.2%). One hundred and seventy-two patients (79.6%) had a PS of 0 to 1. Two hundred fourteen of the 216 patients had received prior docetaxel and platinum therapy. Seventy-nine percent of patients entered the trial due to disease progression on their most recent chemotherapy regimen and 17.6% entered due to unacceptable toxicity from their most recent chemotherapy regimen (most commonly, peripheral neuropathy). Overall, the 2 dose groups were balanced with respect to demographic, disease, and prior treatment characteristics.

A total of 177 patients (81.9%) withdrew from trial treatment; the most common reasons for withdrawal were objective disease progression (150 patients [69.4% of those treated]) and adverse events (16 patients [7.4% of those treated]).

Thirty-five patients were excluded from the PP population because of major protocol violations or deviations, including 16 patients who were not evaluable because of the absence of LCS data beyond baseline. Thus, there were 216 patients in the ITT population and 181 patients in the PP population.

Efficacy:

Overall findings were similar for both the ITT and PP populations. ITT results are presented below.

Objective tumor response rate: The investigator's assessment of best overall objective tumor response is shown in Table I.

The objective tumor response rate for the 250-mg/day group was 11.8% (95%CI: 6.2%, 19.7%), which was significantly greater than 5% (p=0.005, 1-sided). The tumor response rate (8.8%, 95% CI: 4.3%, 15.5%) in the 500-mg/day group was not statistically significantly greater than 5%, but the response rates for both dose groups were similar and had overlapping confidence intervals.

Changes in disease-related symptoms: The symptom improvement rates were similar for the 2 dose groups: 43.1% (95% CI: 33.4%, 53.3%) for the 250-mg/day group, and 35.1% (95%CI: 26.4%, 44.6%) for the 500-mg/day group. Both of these rates were significantly greater than 5%, ($p<0.0001$, 1-sided). Patients with objective tumor response were likely to have a best overall symptom response of "improved" (95.5%), while patients with a best overall response of stable disease also had symptom improvement (71.0%). In sum, 77.4% of the patients with disease control (PR+PRNM+SD) experienced symptom improvement, whereas patients with progressive disease had a low symptom response rate (16.8%).

The time to symptom improvement was similar for each dose group, with a median of 10 days (250-mg/day group) and 9 days (500-mg/day group), ie, at the first measurement post-baseline. Patients exhibiting disease control experienced a median symptom (LCS) time to worsening at 146 days, while those who did not exhibit disease control experienced a median symptom (LCS) time to worsening at 41 days.

Disease control rate: The disease control rates were similar for the 2 dose groups: 42.2% (95% CI: 32.4%, 52.3%) for the 250-mg/day group, and 36.0% (95% CI: 27.2%, 45.5%) for the 500-mg/day group. Median duration of disease control was 125 days for the 250-mg/day group, and 111 days for the 500-mg/day group.

QOL: Improvement rates were marginally higher in the 250-mg/day than in the 500-mg/day group: for TOI they were 33.3% (95% CI: 24.3%, 43.4%) and 20.2% (95% CI: 13.2%, 28.7%), respectively, and for FACT-L they were 34.3% (95% CI: 25.2%, 44.4%) and 22.8% (95% CI: 15.5%, 31.6%), respectively.

The improvement in total FACT-L and TOI scores was associated with improvement in disease-related symptoms, as measured by the LCS.

Progression-free survival and survival: The median number of progression-free survival days was similar for the 2 dose groups: 59 days (95% CI: 56 days, 86 days) for the 250-mg/day group, and 60 days (95% CI: 49 days, 67 days) for the 500-mg/day group.

With a minimum follow-up of 4 months, median survival was similar between the 2 dose groups, 185 days for the 250-mg/day group compared to 183 days for the 500-mg/day group.

Table I Investigator's assessment of best overall objective response in the ITT population

Best overall response (number [%] of patients)	Randomized treatment	
	ZD1839 250 mg/day (n=102)	ZD1839 500 mg/day (n=114)
Response		
Complete response	0 (0.0)	0 (0.0)
Partial response	9 (8.8)	9 (7.9)
Partial response in non-measurable disease	3 (2.9)	1 (0.9)
Total	**12 (11.8)**	**10 (8.8)**
No response		
Stable disease	31 (30.4)	31 (27.2)
Progression (ie, disease increasing)	54 (52.9)	59 (51.8)
Not assessable[a]	0 (0.0)	5 (4.4)
Unknown[b]	5 (4.9)	9 (7.9)
Total	**90 (88.2)**	**104 (91.2)**

[a] Marker lesions were obscured by pleural fluid and/or ascites.
[b] Patients that did not have complete tumor assessments at Day 28 and Day 56 visits to clearly allow determination of response.

Safety: Both the number of days on trial and the number of days on treatment (excluding days off therapy) were comparable in the 250-mg/day and 500-mg/day groups. The mean number of days on ZD1839 treatment (72.6 days and 62.7 days, respectively) was similar to the mean number of days on trial (75.7 days and 69.5 days, respectively) for both doses, indicating that the average duration of treatment interruptions was short in both groups. The proportion of patients who had an interruption in therapy or who had a dose reduction due to toxicity was lower in the 250-mg/day group than in the 500-mg/day group (14.7% versus 22.8% for interruption in therapy; 1.0% versus 8.8% for dose reduction).

Nearly all patients had at least 1 adverse event (98.6%), and the majority of patients (79.2%) had at least 1 adverse event that was considered by the investigator to be drug-related. The percentage of patients who had drug-related events was lower in the 250-mg/day group than in the 500-mg/day group (72.5% versus 85.1%). The most common drug-related adverse events reported by at least 10% of patients in the 250-mg/day group were diarrhea (48.0%), rash (43.1%), acne (24.5%), dry skin and nausea (12.7% for each), and vomiting (11.8%). These events were also the most common events in the 500-mg/day group, and the incidence of each was lower at 250 mg/day than at 500 mg/day, with the exception of vomiting (which had a similar incidence in the 2 groups). In general, the first occurrence of adverse events was in the first treatment period. There was no evidence of any cumulative toxicity, and in general, drug-related adverse events were reversible.

In the 250-mg/day group, the incidence of CTC Grade 3 or 4 adverse events (40.2%) and withdrawals due to adverse events (3.9%) was slightly lower than in the 500-mg/day group (46.5% and 9.6%, respectively). Similarly, in the 250-mg/day group, the incidence of

drug-related CTC Grade 3 or 4 adverse events (6.9%) and withdrawals due to drug-related adverse events (1.0%), was lower than for the 500-mg/day group (17.5% and 4.4%, respectively). The incidence of both serious adverse events and drug-related serious adverse events was similar in the 2 dose groups.

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