SUMMARY

ASTRAZENECA

FINISHED PRODUCT: IRESSA™

ACTIVE INGREDIENT: ZD1839

Trial title (number): A randomized, double-blind, parallel-group, Phase II, multicenter trial to assess the efficacy of ZD1839 (IRESSA™) 250 and 500 mg/day in patients with advanced non-small-cell lung cancer who have failed one or two previous chemotherapy regimens; at least one having contained platinum (1839IL/0016).

Clinical phase: II

First patient recruited: 2 October 2000
Last patient recruited: 30 January 2001
Data cut-off date: 22 May 2001
AstraZeneca approval date: 17 October 2001

Principal investigators and location (center numbers):

Publications: None at the time of preparing this report.

OBJECTIVES

Primary objectives: To evaluate the objective tumor response rates for each 250 mg and 500 mg daily dose of ZD1839; and to further characterize the safety profile of ZD1839 for each 250 mg and 500 mg daily dose of ZD1839.

Secondary objectives: To estimate symptom improvement rates and time to symptom worsening; to estimate disease control rates; to evaluate changes in Quality of Life (QOL); to estimate progression-free survival and survival; to assess whether there were differences for Japanese and non-Japanese patients with respect to efficacy and safety, by dose and overall; 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.

METHODS

Design: This was a randomized, double-blind, parallel group, Phase II multicenter trial. Patients were randomized into 1 of the 2 treatment groups: ZD1839 250 mg/day or ZD1839 500 mg/day orally. Patients continued their randomized treatment until disease progression, intolerable toxicity, or until any of the withdrawal criteria were met. Four months (16 weeks) after the last patient was randomized into the trial, the data were analyzed. Patients continuing to show evidence of response or disease stabilization due to ZD1839 therapy upon unblinding, could continue ZD1839 administration (depending on their randomized dose of ZD1839) by being registered in Trial 1839IL/0026. All patients, whether they were registered into Trial 1839IL/0026 or not, were followed for survival.

Population: Two-hundred patients were to be recruited: 100 Japanese and 100 non-Japanese patients with advanced non-small-cell lung cancer (NSCLC) who had failed 1 or 2 previous chemotherapy regimens (at least 1 of these having contained platinum).

Key inclusion criteria: Aged 18 years or older; histological or cytological confirmation of NSCLC that was locally advanced Stage III or metastatic Stage IV; recurrent or refractory disease after having failed 1 or 2 chemotherapy regimens, at least 1 having contained platinum; at least 1 bi-dimensionally measurable lesion with clearly defined margins, or at least 1 radiographically assessable lesion with margins not clearly defined, a performance status (PS) 0 to 2; a life expectancy of 12 weeks or more.

Key exclusion criteria: More than 2 previous chemotherapy regimens; last dose of systemic anticancer therapy within 21 days before Day 1 of treatment; any unresolved chronic toxicity Common Toxicity Criteria (CTC) Grade 2 from previous anticancer therapy (except for alopecia); radiotherapy completed within 14 days before Day 1 of treatment; incomplete healing from prior oncologic or other major surgery; superior vena cava syndrome; newly diagnosed intracerebral metastases; signs of spinal cord compression; neutrophils $<1.5 \times 10^9$/liter (L) or platelets $<75 \times 10^9$/L; serum bilirubin >1.25 times the upper limit of reference range (ULRR); alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) or aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) >2.5 times the ULRR if no demonstrable liver metastases or >5 times the ULRR in the presence of liver metastases; serum creatinine >1.5 times the ULRR; pregnancy or breast feeding women.

Dosage: ZD1839 250 mg once daily (od), ZD1839 500 mg od. Each daily dose of 250 mg ZD1839 was comprised of 1 x ZD1839 250-mg tablet and 1 size-matched placebo tablet. Each daily dose of 500 mg of ZD1839 was comprised of 2 x ZD1839 250-mg tablets. Trial treatment was administered once a day, at approximately the same time every morning. On Day 1 of Treatment Period 1 only, patients received 2 doses of their randomized treatment. For all subsequent doses, trial treatment was to be taken once daily. If a patient experienced unacceptable toxicity, the dose could be reduced by approximately 50% and the patient was to continue with the adjusted dose until the end of the trial. Formulation and batch numbers were: ZD1839 250-mg tablets, F12653 (batch numbers 71026B00, 63433G99, and 71403J00); ZD1839 100-mg tablets for dose reduction only, F12651 (batch number 63432J99); and placebo tablets, F12647 (batch numbers 70356D00, 71752K00, and 63430E99).

Key assessments:
Efficacy: The primary efficacy endpoint was objective tumor response (complete response [CR], partial response [PR], and partial response in non-measurable disease [PRNM]). Tumor assessments were done every 4 weeks after the start of treatment, and then every 8 weeks following the fourth 28-day treatment period. Upon withdrawal, or at data cut-off for ongoing patients, the investigator assigned a best overall response for the patient.
Upon completion of the trial, images of patients were sent for independent review to a Response Evaluation Committee (REC). Reviewers were blinded to treatment, but not to the sequence of clinical visits. The REC's conclusions were used to corroborate the analysis from the investigators' assessments. The primary analysis of overall best objective tumor response was based on the investigators' assessments, with the primary analysis population being the evaluable-for-response population (see Table I).

Table I Definition of trial populations

Population	Definition
Intention-to-treat (ITT)	All patients who received at least 1 dose of trial drug
Per-protocol (PP)	A subset of the intention-to-treat population. Included patients who did not significantly violate (ie, inclusion/exclusion criteria) or significantly deviate from the protocol
Evaluable-for-response	A subset of the per-protocol population. Included patients who received a minimum of 14 days of trial treatment in every 28-day treatment period[a] before the first tumor assessment documenting their best tumor response
Evaluable-for-symptom improvement	A subset of the per-protocol population. Included patients with a baseline LCS score of 24 or less

[a] When the treatment period was not exactly 28 days, the 14-day rule still applied.
LCS Lung Cancer Subscale.

The secondary efficacy endpoints were:

- disease-related symptoms: these were assessed using a diary card consisting of the 7-item Lung Cancer Subscale (LCS) from the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire. Each week on treatment, patients completed the diary card to record the presence or absence of disease-related symptoms, and their severity. At baseline and on Day 28 of each treatment period, symptoms were recorded on the LCS within the FACT-L questionnaire.
- disease control (CR, PR, PRNM, and stable disease [SD])
- QOL using the FACT-L questionnaire, and the Treatment Outcome Index (TOI) which is a sum of the scores from the physical well-being, functional well-being, and LCS domains of the FACT-L
- progression-free survival ie, the time from randomization to objective disease progression
- overall survival ie, the time from randomization to death

Differences were assessed between the Japanese and non-Japanese patients in this trial with respect to the primary and secondary efficacy endpoints described above.

EGFR data were not available for inclusion in this report. Consequently, these data, and the correlation of EGFR expression in tumor biopsies and the probability of tumor response, will be presented in a separate report.

Pharmacokinetics: The secondary pharmacokinetics endpoint was trough plasma concentrations of ZD1839. These data were used to perform a population analysis.

Safety: All patients who received ZD1839 were included in the assessment of safety. The primary safety endpoint was adverse events (AEs). The frequency and severity of AEs has been presented in this report. Clinical laboratory data were also collected and reported.

RESULTS

Demography: Two-hundred-and-ten patients from 43 centers entered this trial: 108 patients at 24 non-Japanese centers, and 102 patients at 19 Japanese centers. The first patient was randomized on 2 October 2000, and the last patient was randomized on 30 January 2001.

The last patient visit took place on the data cut-off date (22 May 2001); on this date, 53 (25.2%) patients were continuing in the trial.

Demographic and disease characteristics are presented in Table II. The mean age of patients in the trial was 59.6 years (range 28 to 85 years); 70.5% were men, and 48.6% were Caucasian and 48.6% were Japanese. The predominant tumor type and stage at trial entry were adenocarcinoma (62.9%) and Stage IV (80.5%). As protocolled, all patients had failed at least 1 previous chemotherapy regimen containing platinum; 43.8% had failed 2 previous chemotherapy regimens. One-hundred-and-eighty-three patients (87.1%) had a PS of 0 to 1.

Similar numbers of patients were randomized into the 2 dose groups: 104 in the 250-mg/day group, and 106 in the 500-mg/day group. There was a lower number of women (25.0%) in the 250-mg/day group than in the 500-mg/day group (34.0%). In addition, there were small imbalances between the two dose groups regarding the numbers of patients typed with squamous or undifferentiated tumors (see Table II).

Of the 74.8% of patients who withdrew from trial treatment, 62.4% were due to objective disease progression, and 9.0% were due to adverse events.

A total of 209 patients were included in the ITT population, and 208 patients were included in the PP and evaluable-for-response populations.

Table II Demographic and disease characteristics of patients at trial entry

Characteristic	Randomized treatment			Strata					
				Non-Japanese patients			Japanese patients		
	ZD1839 250 mg/day (n=104)	ZD1839 500 mg/day (n=106)	All patients (n=210)	ZD1839 250 mg/day (n=53)	ZD1839 500 mg/day (n=55)	All patients (n=108)	ZD1839 250 mg/day (n=51)	ZD1839 500 mg/day (n=51)	All patients (n=102)
Age (years)									
Mean (standard deviation)	60.3 (9.5)	58.9 (9.7)	59.6 (9.6)	59.5 (9.1)	59.7 (9.8)	59.6 (9.4)	61.1 (9.9)	57.9 (9.5)	59.5 (9.8)
Median	61.0	60.0	60.0	60.0	61.0	60.5	61.0	59.0	60.0
Range	28 to 85	37 to 78	28 to 85	42 to 85	38 to 78	38 to 85	28 to 77	37 to 76	28 to 77
Sex (number [%] of patients)									
Women	26 (25.0)	36 (34.0)	62 (29.5)	10 (18.9)	14 (25.5)	24 (22.2)	16 (31.4)	22 (43.1)	38 (37.3)
Men	78 (75.0)	70 (66.0)	148 (70.5)	43 (81.1)	41 (74.5)	84 (77.8)	35 (68.6)	29 (56.9)	64 (62.7)
Race (number [%] of patients)									
Caucasian	49 (47.1)	53 (50.0)	102 (48.6)	49 (92.5)	53 (96.4)	102 (94.4)	0 (0)	0 (0)	0 (0)
Black	2 (1.9)	0 (0)	2 (1.0)	2 (3.8)	0 (0)	2 (1.9)	0 (0)	0 (0)	0 (0)
Hispanic	2 (1.9)	0 (0)	2 (1.0)	2 (3.8)	0 (0)	2 (1.9)	0 (0)	0 (0)	0 (0)
Oriental	0 (0)	1 (0.9)	1 (0.5)	0 (0)	1 (1.8)	1 (0.9)	0 (0)	0 (0)	0 (0)
Japanese	51 (49.0)	51 (48.1)	102 (48.6)	0 (0)	0 (0)	0 (0)	51 (100.0)	51 (100.0)	102 (100.0)
Other[c]	0 (0)	1 (0.9)	1 (0.5)	0 (0)	1 (1.8)	1 (0.9)	0 (0)	0 (0)	0 (0)
Previous cancer treatment (number [%] of patients)									
Failed 1 previous regimen	104 (100.0)	106 (100.0)	210 (100.0)	53 (100.0)	55 (100.0)	108 (100.0)	51 (100.0)	51 (100.0)	102 (100.0)
Failed 2 previous regimens	46 (44.2)	46 (43.4)	92 (43.8)	22 (41.5)	22 (40.0)	44 (40.7)	24 (47.1)	24 (47.1)	48 (47.1)
Radiotherapy	52 (50.0)	48 (45.3)	100 (47.6)	33 (62.3)	30 (54.5)	63 (58.3)	19 (37.3)	18 (35.3)	37 (36.3)
Surgery	32 (30.8)	25 (23.6)	57 (27.1)	21 (39.6)	15 (27.3)	36 (33.3)	11 (21.6)	10 (19.6)	21 (20.6)
Other	4 (3.8)	9 (8.5)	13 (6.2)	0 (0)	0 (0)	0 (0)	4 (7.8)	9 (17.6)	13 (12.7)

Characteristic	Randomized treatment			Strata					
				Non-Japanese patients			Japanese patients		
	ZD1839 250 mg/day (n=104)	ZD1839 500 mg/day (n=106)	All patients (n=210)	ZD1839 250 mg/day (n=53)	ZD1839 500 mg/day (n=55)	All patients (n=108)	ZD1839 250 mg/day (n=51)	ZD1839 500 mg/day (n=51)	All patients (n=102)
WHO performance status (number [%] of patients)									
Normal activity (0)	18 (17.3)	20 (18.9)	38 (18.1)	9 (17.0)	8 (14.5)	17 (15.7)	9 (17.6)	12 (23.5)	21 (20.6)
Restricted activity (1)	73 (70.2)	72 (67.9)	145 (69.0)	34 (64.2)	39 (70.9)	73 (67.6)	39 (76.5)	33 (64.7)	72 (70.6)
In bed ≤50% of the time (2)	13 (12.5)	14 (13.2)	27 (12.9)	10 (18.9)	8 (14.5)	18 (16.7)	3 (5.9)	6 (11.8)	9 (8.8)
Histology type (number [%] of patients)									
Adenocarcinoma	64 (61.5)	68 (64.2)	132 (62.9)	26 (49.1)	28 (50.9)	54 (50.0)	38 (74.5)	40 (78.4)	78 (76.5)
Squamous	25 (24.0)	18 (17.0)	43 (20.5)	16 (30.2)	9 (16.4)	25 (23.1)	9 (17.6)	9 (17.6)	18 (17.6)
Large cell	9 (8.7)	9 (8.5)	18 (8.6)	7 (13.2)	7 (12.7)	14 (13.0)	2 (3.9)	2 (3.9)	4 (3.9)
Undifferentiated	3 (2.9)	8 (7.5)	11 (5.2)	2 (3.8)	8 (14.5)	10 (9.3)	1 (2.0)	0 (0)	1 (1.0)
Squamous and adenocarcinoma	3 (2.9)	3 (2.8)	6 (2.9)	2 (3.8)	3 (5.5)	5 (4.6)	1 (2.0)	0 (0)	1 (1.0)
Stage classification (number [%] of patients)									
IIIA	4 (3.8)	2 (1.9)	6 (2.9)	1 (1.9)	0 (0)	1 (0.9)	3 (5.9)	2 (3.9)	5 (4.9)
IIIB	19 (18.3)	16 (15.1)	35 (16.7)	14 (26.4)	6 (10.9)	20 (18.5)	5 (9.8)	10 (19.6)	15 (14.7)
IV	81 (77.9)	88 (83.0)	169 (80.5)	38 (71.7)	49 (89.1)	87 (80.6)	43 (84.3)	39 (76.5)	82 (80.4)
Metastatic status (number [%] of patients)									
M0	25 (24.0)	20 (18.9)	45 (21.4)	17 (32.1)	8 (14.5)	25 (23.1)	8 (15.7)	12 (23.5)	20 (19.6)
M1	79 (76.0)	86 (81.1)	165 (78.6)	36 (67.9)	47 (85.5)	83 (76.9)	43 (84.3)	39 (76.5)	82 (80.4)

Efficacy:

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

The objective tumor response rates were similar for the 2 dose groups: 18.4% (95% CI: 11.5%, 27.3%) for the 250-mg/day group, and 19.0% (95% CI: 12.1%, 27.9%) for the 500-mg/day group. The overall response rate was 18.7%, and the majority of responses (87.1%) were ongoing at data cut-off.

Results from the independent REC were generally in agreement with the results of the trial. From the REC's independent readings of 107 patients assessed by the investigators as having CR, PR, PRNM or SD (including 38 of the 39 responders), 34 patients were assessed as being responders.

Changes in disease-related symptoms: The symptom improvement rates were similar for the 2 dose groups: 40.3% (95% CI: 28.5%, 53.0%) for the 250-mg/day group, and 37.0% (95% CI: 26.0%, 49.1%) for the 500-mg/day group. The overall symptom improvement rate was 38.6%. Patients with objective tumor response were more likely to have a best overall symptom response of "improved" (77.8%) than patients without a tumor response (29.2%). In addition, more than half the patients (53.3%) with stable disease experienced symptom improvement, whereas patients with progressive disease usually did not show any benefits in symptoms.

The time to symptom improvement was similar for each dose group with a median of 8 days ie, at the first measurement post-baseline. Time to symptom worsening could not be calculated for each dose due to insufficient numbers of patients worsening by the time of the data cut-off.

Disease control rate: The disease control rates were similar for the 2 dose groups: 54.4% (95% CI: 44.3%, 64.2%) for the 250-mg/day group, and 51.4% (95% CI: 41.5%, 61.3%) for the 500-mg/day group. Median duration of disease control was 98 days for the 250-mg/day group, and 140 days for the 500-mg/day group.

QOL: Improvement rates were similar for the 250-mg/day and 500-mg/day groups: for TOI they were 20.9% (95% CI: 11.9%, 32.6%) and 17.8% (95% CI: 9.8%, 28.5%), respectively, and for FACT-L they were 23.9% (95% CI: 14.3%, 35.9%) and 21.9% (95% CI: 13.1%, 33.1%), respectively. The overall QOL improvement rates were 19.3% for TOI, and 22.9% for FACT-L. Patients with objective tumor response were more likely to have a best overall response of "improved" in TOI and FACT-L (both 51.9%) than patients without a tumor response (11.5% and 15.9%, respectively).

Improvements in TOI and FACT-L happened rapidly with a median time to improvement of 29 days ie, at the first measurement post-baseline.

Progression-free survival and survival: The median number of progression-free survival days was similar for the 2 dose groups: 83 days (95% CI: 61 days, 86 days) for the 250-mg/day group, and 85 days (95% CI: 59 days, 116 days) for 500-mg/day group.

With a minimum follow-up of 4 months, median survival was not calculable for all groups due to insufficient events; 68% of patients in the 250-mg/day group were alive at 4 months compared to 79% in the 500-mg/day group.

Table III Investigator's assessment of best overall objective response: evaluable-for-response population

Best overall response (number [%] of patients)	Randomized treatment			Strata					
				Non-Japanese patients			Japanese patients		
	ZD1839 250 mg/day (n=103)	ZD1839 500 mg/day (n=105)	All patients (n=208)	ZD1839 250 mg/day (n=52)	ZD1839 500 mg/day (n=54)	All patients (n=106)	ZD1839 250 mg/day (n=51)	ZD1839 500 mg/day (n=51)	All patients (n=102)
Response									
Complete response	0 (0)	1 (1.0)	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)	1 (1.0)
Partial response	18 (17.5)	19 (18.1)	37 (17.8)	5 (9.6)	6 (11.1)	11 (10.4)	13 (25.5)	13 (25.5)	26 (25.5)
Partial response in non-measurable disease	1 (1.0)	0 (0)	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)	1 (1.0)
Total	**19 (18.4)**	**20 (19.0)**	**39 (18.7)**	**5 (9.6)**	**6 (11.1)**	**11 (10.4)**	**14 (27.5)**	**14 (27.5)**	**28 (27.5)**
No response									
Stable or no response	37 (35.9)	34 (32.4)	71 (34.1)	15 (28.8)	17 (31.5)	32 (30.2)	22 (43.1)	17 (33.3)	39 (38.2)
Progression (ie, disease increasing)	42 (40.8)	44 (41.9)	86 (41.3)	28 (53.8)	26 (48.1)	54 (50.9)	14 (27.5)	18 (35.3)	32 (31.4)
Unknown	5 (4.9)	7 (6.7)	12 (5.8)	4 (7.7)	5 (9.3)	9 (8.5)	1 (2.0)	2 (3.9)	3 (2.9)
Total	**84 (81.6)**	**85 (81.0)**	**169 (81.2)**	**47 (90.4)**	**48 (88.9)**	**95 (89.6)**	**37 (72.5)**	**37 (72.5)**	**74 (72.5)**

Demography and efficacy in Japanese and non-Japanese patients: There were a number of imbalances at trial entry between the Japanese and non-Japanese patient populations (see Table II):

- There were fewer women in the non-Japanese population (22.2%) compared to the Japanese population (37.3%).
- More non-Japanese patients had received radiotherapy (58.3%) and surgery (33.3%) than Japanese patients (36.3% and 20.6%, respectively).
- More non-Japanese patients had a PS of 2 (16.7%) compared with Japanese patients (8.8%).
- The predominant histology type was adenocarcinoma, however, more Japanese patients had adenocarcinoma (76.5%) than non-Japanese patients (50.0%). The proportion of patients with squamous cell histology was similar between the 2 populations. Large cell and undifferentiated histologies were less frequent in the Japanese patients (3.9% and 1.0%, respectively) than in the non-Japanese patients (13.0% and 9.3%, respectively).

For the primary endpoint, objective tumor responses were seen in all 4 strata: response rates for non-Japanese patients were 9.6% (95% CI: 3.2%, 21.0%) for the 250-mg/day stratum, and 11.1% (95% CI: 4.2%, 22.6%) for the 500-mg/day stratum. The response rate for Japanese patients was 27.5% (95% CI: 15.9%, 41.7%) for both dose strata. The lower 95% CI for the Japanese strata indicated that the true response rate was >5%, however, the lower 95% CI for the non-Japanese strata failed to show that the true response rate was >5%.

Significant differences were observed between Japanese and non-Japanese patients with respect to tumor response, disease control, progression-free survival, and overall survival. Multivariate analyses showed that, as expected, a portion of the differences were confounded with imbalances in baseline factors. This suggests that a portion of the remaining differences could be explained by imbalances in unknown prognostic factors as a result of patient selection rather than a true ethnic difference. Thus, the results regarding a potential ethnic difference were inconclusive due to the non-randomized comparison, and the limitations of the data.

Pharmacokinetics: The conclusions from the population analysis were as follows:

- There was approximate proportionality between the 250-mg/day and 500-mg/day doses with respect to the mean population predicted trough plasma concentration of ZD1839.
- No clinically relevant covariates were identified.
- No clear effect of patient's co-medication on the predicted trough concentration was observed.
- There was no correlation between efficacy and the predicted trough concentration.
- Correlation was identified between the predicted trough concentrations and the incidence of diarrhea, acne and/or rash, and pruritus. There was no clear correlation to patients showing increased levels of SGOT/AST and SGPT/ALT, and nausea and/or vomiting.
- Considerable overlap was identified in the predicted steady-state trough concentrations between Japanese and non-Japanese patients; there was no statistically significant difference ($p>0.8$) between Japanese and non-Japanese steady-state trough concentrations.

Safety: The mean number of days on ZD1839 treatment for patients on the 250-mg/day and 500-mg/day doses was 85.1 days and 81.5 days, respectively. These were similar to the mean number of days on trial for both doses (87.0 days and 86.9 days, respectively), suggesting that patients

were compliant in taking their randomized treatment as instructed. There were less dose interruptions for the 250-mg/day dose than for the 500-mg/day dose; these were spread throughout the treatment periods with similar numbers of patients in both the non-Japanese and Japanese groups. No patients in the 250-mg/day group had dose reductions compared with 11 patients in the 500-mg/day group.

The overview of adverse events is presented in Table IV. Overall, most patients experienced at least 1 adverse event (99.0%). Of these, 91% had drug-related adverse events. The most frequent drug-related adverse events experienced by at least 10% of patients receiving ZD1839 250-mg/day were rash (46.6%), diarrhea (39.8%) pruritus (30.1%), dry skin (27.2%), nausea (12.6%), acne (12.6%), SGPT/ALT increased (12.6%), and SGOT/AST increased (10.7%). Patients receiving ZD1839 500 mg/day also experienced the following drug-related adverse events with a frequency of ≥10%: vomiting (19.8%), anorexia (18.9%), pain (16.0%), and asthenia (10.4%). The majority of drug-related adverse events with an overall incidence of at least 5% were reported less frequently at the 250-mg/day dose than at the 500-mg/day dose. 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, adverse events were reversible.

There were 5 (2.4%) adverse events with an outcome of death. Four of these deaths occurred on the 250-mg/day dose, and 1 on the 500-mg/day dose. None of these adverse events were considered by the investigator to be related to ZD1839. For 1 patient (0207/0001), the investigator felt unable to assign causality.

In the 250-mg/day group, the incidence of CTC Grade 3 or 4 adverse events (32.0%), serious adverse events (20.4%), and withdrawals due to adverse events (6.8%), was lower than for the 500-mg/day group (50.9%, 25.5%, and 11.3%, respectively). Similarly, in the 250-mg/day group, the incidence of drug-related CTC Grade 3 or 4 adverse events (8.7%), serious drug-related adverse events (2.9%), and withdrawals due to drug-related adverse events (1.9%), was lower than for the 500-mg/day group (30.2%, 11.3%, and 9.4%, respectively)

There was no evidence of hematological, ophthalmologic, cardiac or renal toxicity.

In terms of absolute adverse event numbers, more events were reported by the Japanese patient population. Allowing for cultural and baseline variables, the safety profiles between the 2 ethnic groups appeared similar.

Table IV Overview of adverse events: intention-to-treat population

Category[a] (number [%] of patients)	Randomized treatment			Strata					
				Non-Japanese			Japanese		
	ZD1839 250 mg/day (n=103)	ZD1839 500 mg/day (n=106)	All patients (n=209)	ZD1839 250 mg/day (n=52)	ZD1839 500 mg/day (n=55)	All patients (n=107)	ZD1839 250 mg/day (n=51)	ZD1839 500 mg/day (n=51)	All patients (n=102)
Patients with an adverse event	101 (98.1)	106 (100.0)	207 (99.0)	50 (96.2)	55 (100)	105 (98.1)	51 (100)	51 (100)	102 (100)
Drug-related adverse event(s)	88 (85.4)	102 (96.2)	190 (90.9)	38 (73.1)	51 (92.7)	89 (83.2)	50 (98.0)	51 (100)	101 (99.0)
Deaths									
Due to adverse event(s)	4 (3.9)	1 (0.9)	5 (2.4)	3 (5.8)	1 (1.8)	4 (3.7)	1 (2.0)	0 (0)	1 (1.0)
Due to a drug-related adverse event(s)	0 (0)	1 (0.9)	1 (0.5)	0 (0)	1 (1.8)	1 (0.9)	0 (0)	0 (0)	0 (0)
Withdrawals									
Due to an adverse event(s)	7 (6.8)	12 (11.3)	19 (9.1)	4 (7.7)	4 (7.3)	8 (7.5)	3 (5.9)	8 (15.7)	11 (10.8)
Due to a drug-related adverse event(s)	2 (1.9)	10 (9.4)	12 (5.7)	1 (1.9)	3 (5.5)	4 (3.7)	1 (2.0)	7 (13.7)	8 (7.8)
Due to a serious adverse event(s)	6 (5.8)	6 (5.7)	12 (5.7)	4 (7.7)	2 (3.6)	6 (5.6)	2 (3.9)	4 (7.8)	6 (5.9)
Due to a serious drug-related adverse event(s)	1 (1.0)	4 (3.8)	5 (2.4)	1 (1.9)	1 (1.8)	2 (1.9)	0 (0)	3 (5.9)	3 (2.9)
Serious adverse events	21 (20.4)	27 (25.5)	48 (23.0)	18 (34.6)	21 (38.2)	39 (36.4)	3 (5.9)	6 (11.8)	9 (8.8)
Serious drug-related adverse event(s)	3 (2.9)	12 (11.3)	15 (7.2)	3 (5.8)	7 (12.7)	10 (9.3)	0 (0)	5 (9.8)	5 (4.9)
CTC Grade 3 or 4 adverse event(s)	33 (32.0)	54 (50.9)	87 (41.6)	24 (46.2)	35 (63.6)	59 (55.1)	9 (17.6)	19 (37.3)	28 (27.5)
Drug-related CTC Grade 3 or 4 adverse event(s)	9 (8.7)	32 (30.2)	41 (19.6)	3 (5.8)	16 (29.1)	19 (17.8)	6 (11.8)	16 (31.4)	22 (21.6)

[a] Categories are not mutually exclusive; patients may have adverse events in more than 1 category.
CTC Common toxicity criteria.