CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-399

Medical Review(s)

Clinical Review
NDA 21-399

Drug Name	
Medical Reviewer	**Martin H. Cohen, M.D.**
Medical Team Leader	**Isagani Chico, M.D.** **Grant Williams, M.D.**
Documents reviewed	**EDR Submissions**

Table of Contents

Table of Tables

Table of Figures

Executive Summary

I. Recommendations

A. Approvability

On September 24, 2002 Iressa was presented to ODAC. Two major questions were asked.

"Given the lack of clinical benefit in two large studies of ZD1839 in combination with standard first-line NSCLC chemotherapy, is the Study 0039 response rate of 10% in 139 patients with resistant or refractory NSCLC reasonably likely to predict ZD1839 clinical benefit in NSCLC?" The vote was 11 **yes** votes and 3 **no.**

By the above vote the Committee indicated that, for NSCLC in the third line setting where there are no viable treatment options, a 10% response rate is meaningful, and shows evidence of biologic activity of the drug. The reason for failure of the first line trials remains unexplained, and requires further study.

The ODAC was also asked to evaluate whether ZD1839 treatment was associated with symptom benefit? The Committee, by a vote of 9-Yes and 5-No felt that the symptom data supported only a soft claim of symptom management, and that a randomized, controlled trial with a "no drug" arm (either placebo or best supportive care) would be required for substantial evidence.

The Medical Officer concurs with the ODAC decision and recommends approval of ZD1839 for the treatment of patients with locally advanced or metastatic NSCLC in whom platinum-based and docetaxel chemotherapies have failed. ZD1839 should not be used in combination with doublet, platinum based chemotherapy in the first-line treatment of NSCLC.

B. Phase IV Studies

Studies proposed as phase IV commitments under Subpart H are summarized in the following table.

Study type	Study pts.	Sample Size (N)	Design	1^0 endpoint	2^0 endpoint	Completion date
Adjuvant	Stage IB, II, III Resected	1160	Double-blind Placebo control	OS	DFS	10/07
Maintenance	Stage III Inoperable	840	Double-blind Placebo control	OS & PFS	–	5/06
First-line	Stage III/IV PS 2-3 LCS ≤20 Medical conditions	207	Double-blind BSC control	Symptom improvement	OS TTP	9/06
Refractory	Stage III/IV PS 0-3	624	Double-blind BSC control	OS	PFS Symptoms	9/06
Refractory	Stage III/IV PS 0-2 LCS ≤20	207	Double-blind BSC control	Symptom improvement	OS TTP	9/06

BSC=best supportive care; DFS=disease free survival; LCS= Lung cancer subscale;
PFS=progression free survival;
PS=performance status; OS=overall survival

The proposed phase 4 studies are adequate. It is recommended that the two symptom improvement studies be powered for a conventional endpoint, either overall survival or time to progression. This is because of a multiplicity of issues involving evaluation of the Lung Cancer Subscale (LCS).

II Summary of Clinical Findings

A. Overview of Clinical Program

ZD 1839 (Iressa™) is a new class of drug that inhibits tyrosine kinase activity including the Epidermal Growth Factor Receptor (EGFR). The present NDA is a rolling submission, the last section of which was submitted August 5, 2002. The NDA is seeking accelerated approval for Iressa as monotherapy for patients receiving third line treatment for non-small cell lung cancer.

At present, there are three cisplatin-containing doublets approved for the first-line therapy of patients with locally advanced or metastatic non-small cell lung cancer (cisplatin/vinorelbine, cisplatin/paclitaxel and cisplatin/gemcitabine), and a single drug, docetaxel approved for the second-line treatment of the same patient population. Third-line treatment regimen is an unmet need.

Of the two clinical trials submitted by the sponsor, Trial 39, titled "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", addresses that unmet need. Trial 16, titled "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 is primarily a second-line trial.

There was agreement between the FDA and the sponsor that all patients enrolled into Trial 39 must have received prior treatment with at least two chemotherapy regimens which were platinum- and docetaxel-based (platinum and docetaxel need not be given concurrently). Failure of prior chemotherapy must have been the result of disease progression within 90 days of the last dose of chemotherapy or treatment intolerance.

The quality of life evaluation was initially considered by the FDA to be exploratory. At a later time, however, FDA stated that quality of life is acceptable from a statistical standpoint, as a "co-primary" endpoint. However, it would be necessary to demonstrate that the symptom findings are credible in a single arm study and are clinically significant. Correlation with objective response may be helpful in this regard.

Both trials randomized patients to either ZD1839 250 mg/day or to 500 mg/day. The primary objectives of Trial 39 were to evaluate objective tumor response rate and symptom improvement rate. The primary objective of Trial 16 was to evaluate objective tumor response rate. Symptom improvement rate was a secondary objective.

The first patient was recruited to Trial 39 on 7 November 2000, the last on 6 April 2001. The total intent to treat accrual was 216 patients from 30 US centers.

Trial 39 patients had performance status 0 to 2. Patients were required to be symptomatic from NSCLC as evidenced by a score of 24 points or less (asymptomatic score 28) on the lung cancer subscale (LCS) of the functional assessment of cancer therapy-lung (FACT–L) questionnaire.

The following paragraphs include efficacy results as summarized by the sponsor and efficacy results determined from the FDA analysis.

B. Efficacy

B.1. Efficacy (per sponsor):

A total of 102 Trial 39 patients were treated with ZD1839 250 mg/day, and 114 with 500 mg/day. As of the data cutoff date (1 August 2001), 39 patients were continuing in the trial. The median age of Trial 39 treated patients 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. The predominant histology was adenocarcinoma (66.2%). One hundred and seventy-two patients (79.6%) had a PS of 0 to 1. 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]).

For Trial 39 the sponsor reported that the objective tumor response rate for the 250-mg/day group was 11.8% (95%CI: 6.2%, 19.7%). The tumor response rate in the 500-mg/day group was 8.8%, (95% CI: 4.3%, 15.5%). Response rate differences were not statistically significant.

For Trial 39 the sponsor reported that symptom improvement rates (Lung Cancer Subscale [LCS]) 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. 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%).

For Trial 39 QOL was determined by the FACT-L instrument and the Treatment Outcome Index (TOI). The FACT-L questionnaire contains a total of 34 questions, divided into 5 different domains: disease-related symptoms, physical, functional, emotional, and social. Each question is scored from 0 to 4. The Treatment Outcome Index (TOI) is the total score of disease-related symptom, physical, and functional questions. Changes of 6 points or more were found to be meaningful. The complete FACT-L questionnaire was filled out by patients every

28 days at the end of a treatment period. while disease-related symptom scores were obtained on a weekly basis. The overall compliance of filling out the questionnaire was 86%.

The sponsor reported that QOL improvement rates were marginally higher in the 250-mg/day than in the 500-mg/day group: for Treatment Outcome Index (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 Lung Cancer Subscale (LCS).

For Trial 39 the sponsor reported that median progression-free survival 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.

For Trial 16, 210 patients from 43 centers were entered: 108 patients at 24 non-Japanese centers, and 102 patients at 19 Japanese centers. As of the data cut-off date (22 May 2001) 53 (25.2%) patients were continuing in the trial. The mean age of patients in the trial was 59.6 years; 70.5% were men, 48.6% were Caucasian and 48.6% were Japanese. The predominant tumor type was adenocarcinoma (62.9%) and most patients were Stage IV (80.5%).

For Trial 16 the objective response rate for Caucasian patients was 10.8% (11/102) and the response rate of Japanese patients was 27.5% (28/102). Reasons to discount some of these responses will be discussed subsequently in the FDA analysis.
The sponsor analysis of disease related symptoms in Trial 16 patients indicated that 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.

Similarly, sponsor analysis of QOL (Trial 16) indicated that 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.

The median number of progression-free survival days was similar for the 2 Trial 16 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.

In Trial 39 and Trial 16 the majority of patients received ZD1839 for >1 month, with approximately one-third receiving ZD1839 for >3 months. ZD1839 was generally well tolerated at both doses. However, fewer patients on the 250-mg/day dose experienced Grade 3 or 4 drug-related adverse events or withdrew due to drug-related adverse events. There were fewer drug interruptions due to adverse events in the 250-mg/day group (thirty-one patients (15.1%) who received ZD1839 250 mg daily versus 56 patients (25.5%) in the 500-mg/day group. Dose reductions due to toxicity occurred in 0.5% of patients at the 250-mg dose versus 9.5% of patients at the 500-mg dose group.

Drug-related adverse events experienced by at least 10% of patients in the 250-mg/day group were diarrhea, rash, acne, dry skin, nausea, and vomiting SGPT/ALT increased, and SGOT/AST increased. There was no evidence of cumulative toxicity.

B.2. Efficacy (per FDA):

The FDA agrees with an overall response rate of 10.2% in Trial 39 and with an objective response rate of 10.8% (11/102) for Trial 16 Caucasian patients and an objective response rate of 27.5% (28/102) for Trial 16 Japanese patients. There are several bothersome issues raised by the efficacy review of Trials 39 and 16, however. These are considered below.

Study Design: The two submitted randomized trials compared two dose levels of Iressa. There was no comparator treatment regimen. Since both Iressa dose levels displayed comparable efficacy the evaluation of quality of life and symptom relief is problematic.

Study eligibility –In Trial 39 eligible patients must have received at least two prior chemotherapy regimens. They must also have received a platinum agent and docetaxel administered either concurrently or sequentially. Prior regimens must have failed due either to progression while on therapy or because of treatment intolerance. Only 139 of 216 Trial 39 study patients (64%) met these eligibility criteria. Eleven patients (5%) were platinum refractory/intolerant but taxotere sensitive, 58 patients (27%) were taxotere refractory/intolerant but platinum sensitive, and 8 (4%) were not refractory/intolerant to either drug. For each of the above patient groups the response rate was approximately 10%.

For Trial 16, eligibility criteria mandated that patients must have received one, or a maximum of two, prior chemotherapy regimens, one of which must have included platinum. They must also have recurrent or refractory disease. In fact, however, only 35% of study patients were chemotherapy resistant, having progressed on either first- or second-line chemotherapy. Sixty-five percent of study patients had not progressed on prior therapy. Based on the refractoriness to prior chemotherapy, patients in Trial 16 constituted a more favorable group that might be expected to have higher objective response rates than patients in trial 39.

Study patient characteristics -As might be expected from the treatment eligibility requirements of Trial 39, the enrolled study population, (locally advanced or metastatic disease patients who have failed platinum, docetaxel and other chemotherapy and who have a performance status of 0 to 2) is not typical of a population of newly diagnosed NSCLC patients of similar stage and performance status. The latter population might be expected to have a median survival of 6 to 9 months if stage IV at diagnosis and 16 to 18 months if stage III at diagnosis. Patients enrolled in this study have survived for a considerably longer time (48% of patients surviving more than 2 years from initial diagnosis to study randomization). Striking also, is the percent of study patients with adenocarcinoma alone or mixed with squamous cell carcinoma (73.6%). This is expected as adenocarcinoma has the slowest tumor doubling time of all lung cancer histologies. Thus slow growing tumors that produced few to modest systemic effects were selected.

Like patients enrolled into Trial 39, Trial 16 patients had a relatively long time from initial diagnosis to study randomization (median 12.1 months; mean 15.9 months) and also had a high percentage of adenocarcinoma alone (63%) or with other histologies (3%). Thus, this study was also enriched for less aggressive, slowly growing tumors.

Treatment response - Since the large majority of patients enrolled in both trials had stage IV disease it might be expected that patients would have multiple sites of disease and, therefore, multiple measurable lesions. That was not the case. Among the 18 responding patients in trial 39 who had measurable disease (4 responders having evaluable but non-measurable disease) 5 patients had only a single lesion measured and 6 had two lesions measured. As smaller lesions are more likely to respond to chemotherapy than larger lesions, better blood flow, better oxygenation, etc., it was of interest to look at the sum of the areas of measurable lesions in responders. In trial 39, the baseline total tumor area of the measurable lesions was less than 10 cm2 in 5 of 18 responders. In Trial 39 the site of the measurable lesion in patients with only one measurable tumor was lung in 4 patients and liver in one patient. The site of the measurable lesion in patients with two measurable tumors was lung only in 2 patients, lung and liver in 2 patients, lung and lymph node in 1 patient and liver only in 1 patient.

In Trial 16 thirty-eight of the 39 responding patients had measurable lesions. Among the measurable disease patients 16 patients had only a single lesion measured and 12 had two lesions measured. In trial 16 baseline total area of measurable lesions was less than 10 cm2 in 3 of 11 responding Caucasian patients and 11 of 21 responding Japanese patients. Baseline total area of measurable disease was <5 cm2 in 6 responding Japanese patients and no Caucasian patients. In Trial 16 nineteen responders had lung only disease (primary tumor site with or without contralateral lung involvement. The second most common sites of involvement were lung plus regional lymph node disease (6 patients).

Response rate - A widely accepted medical oncology principle is that for each chemotherapy regimen failed the probability of responding to a subsequent regimen decreases and responses are of shorter duration. If we accept this premise then we expect that the Iressa response rate in Trial 39 patients who are refractory to two or more prior chemotherapy regimens should be lower than the response rate of Trial 39 patients who have failed less than two regimens. This was not the case. Response rates of both groups were approximately 10%. Similarly, it is

expected that the response rate of patients in Trial 16 should be higher than the response rate of Trial 39 patients. Caucasian patients in trial 16 also had a 10% response rate. While Japanese patients in Trial 16 had a response rate of 28% there are confounding factors (see above).

Disease Related Symptom improvement – The meaningfulness of the sponsor's evaluation of symptom relief and quality of life is open to question. Because Iressa 250 mg/day and 500 mg/day had comparable efficacy results there was no comparator regimen for QOL/symptom relief analysis. There are also methodologic issues including absence of blinding, early progressors being censored, and the use of concomitant medications that might have contributed to symptom relief.

Overall Conclusions-FDA: An objective response rate of 10.8% in the third-line treatment setting suggests that Iressa has activity in a patient population for whom there is no available therapy. Some of the objective responses were dramatic and there was one complete response. The absence of a non- ZD1839 treated control group is a confounding factor that makes it difficult to fully evaluate the response results. The fact that the study population was enriched for slowly growing, less aggressive cancers further complicates evaluation of results. Other confounding factors are failure to adhere to the eligibility criteria, limited number of measurable lesions, and relatively small tumor volumes (<10 cm2) in 5 of 18 responders who had measurable disease in trial 39 and in 3 of 11 responding Caucasian patients and 11 of 28 responding Japanese patients in Trial 16.

There are fundamental study design issues with the sponsor's quality of life improvement and symptom benefit analyses including absence of a suitable control group, absence of blinding, dropout of patients with early disease progression and meaningfulness of the criteria used to designate benefit. Symptom improvement is obviously an important clinical endpoint. Further effort must take place to improve current instruments and to define clinically meaningful symptomatic endpoints.

C. Safety

ZD1839 was generally well tolerated. Fewer patients on the 250-mg/day dose experienced Grade 3 or 4 drug-related adverse events or withdrew due to drug-related adverse events. There were less drug interruptions due to adverse events in the 250-mg/day group. Dose reductions due to toxicity occurred in only 1.0% of patients at the 250-mg dose versus 8.8% of patients in the 500-mg dose group. Drug-related adverse events experienced by at least 10% of patients in the 250-mg/day group were diarrhea, rash, acne, dry skin, nausea, and vomiting. There was no evidence of cumulative toxicity, and the majority of drug-related adverse events were reversible.

D. Dosing

A dose of 250 mg/day is recommended. Efficacy results were comparable for the 250 mg/d and 500 mg/d ZD1839 treatments and there was less toxicity with ZD1839 250 md/day.

E. Special Populations

Gender: There were no significant differences in safety by gender.

Ethnic origin: Data for patients other than those of White or Japanese origin, is insufficient for analysis. While response rates of Japanese patients were higher than response rates of Caucasian patients ptrognostic factor difference make it difficult to conclude that there are differences in lung cancer behavior and treatment sensitivity in the two populations.

Age: Within each dose there was no significantly different toxicity by age. The small numbers of patients >75 years of age makes it difficult to draw conclusions on this group.

Effect of baseline renal function: ZD1839 and its metabolites are not significantly excreted via the kidney (<4%). No clinical trials have been conducted with ZD1839 in patients with severely compromised renal function.

Effect of baseline hepatic function: Only 5 patients in Trials 39 and 16 had hepatic impairment at trial entry (4 patients with moderate impairment, and 1 patient with severe impairment). Adverse events for these 5 patients are similar to those seen in the overall patient population. Because of small numbers no conclusions should be drawn.

Addendum: On August 19, 2002 the sponsor released the results of their phase III first-line NSCLC studies (INTACT 1 and 2; Iressa NSCLC Trials Assessing Combination Therapy). Two large randomized trials, accruing over 2000 patients, used an add-on design in which patients were randomized to receive either Iressa or placebo together with standard combination chemotherapy, gemcitabine/cisplatin in one study and carboplatin/paclitaxel in the other. At the time of this report study results were mature with approximately 70% of patients having died in each treatment arm. There was no survival benefit from Iressa treatment in either trial. Similarly, secondary endpoints, i.e. response rate and time to progression, also failed to show statistically significant differences. Results were unambiguous.

Clinical Review

1. Introduction and Background

1.1 Proposed Indication, Drug Trade Name, Class, Age Groups

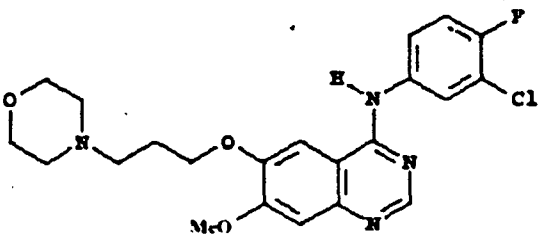
1.1.1 Proposed Indication

IRESSA™ is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer who have previously received platinum-based chemotherapy.

1.1.2 Drug Class

ZD1839 (IRESSA™) is an anilinoquinazoline with the chemical formula N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoline-4-amine and the molecular structure shown in Figure 1. The compound is a white powder with a molecular formula of C22H24ClFN403 and molecular weight of 446.9.

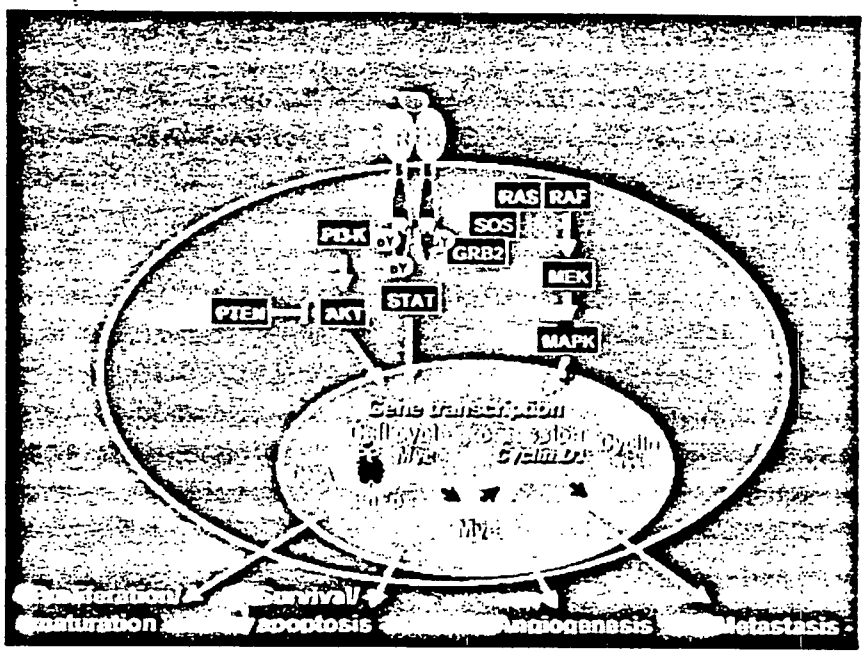
Figure 1: Molecular Structure of ZD1839



1.1.3 ZD1839 mechanism of action

ZD1839 is an inhibitor of EGFR TK activity that completely blocks EGFR autophosphorylation with resultant complete blockade of signal transduction from the EGFR. The EGFR is a member of a sub-family, the HER or erbB family, which includes three other members, erbB2/erbB3/erbB4; HER2(neu)/HER3/HER4), in addition to EGFR. Binding of the cognate ligand, for example, EGF or transforming growth factor cc (TGFcc) to the extracellular domain of EGFR initiates a signal transduction cascade that can influence many aspects of tumor cell biology including growth, survival, metastasis, and angiogenesis, as well as tumor cell sensitivity to chemotherapy and radiation therapy (**Figure 2**).

Figure 2: EGFR Signal Transduction in Tumor cells (Sponsor)



1.2 State of Armamentarium for Indication(s)

There are no approved therapies for stage IIIB/IV ambulatory (PS 0 to 2) NSCLC patients who have progressed on two or more prior regimens (third-line). This is a highly selected population, however, as the large majority of advanced/metastatic NSCLC patients have either died or are non-ambulatory at that point in time. Docetaxel is approved as second-line NSCLC treatment. There are three approved cisplatin containing regimens for first-line NSCLC chemotherapy

1.3 Important Milestones in Product Development

Selected Discussion Between The Food And Drug Administration and the sponsor;

It was agreed that a pivotal trial entitled "A randomized, double blind, parallel-group, Phase II, multicenter trial of 2 doses of ZD1839 in patients with advanced NSCLC who have previously progressed or were intolerant of at least 2 chemotherapy regimens that contained platinum and docetaxel given concurrently or as separate treatment regimens" (Trial ZD18391L/0039, was acceptable as a registration trial in this indication. Trial features include:

- A randomized, 2-dose, double-blind, parallel-group, Phase II, multicenter trial conducted in the United States
- Number of patients: 200
- Two co-primary end points: objective tumor response (complete response and partial response) and disease-related symptom improvement rate

Summary of other development discussions, excluding protocol changes for Trial 39:

A clinical pharmacology program was agreed upon. The highlights of the agreement are as follows:

Since renal clearance is not a major route of excretion for ZD1839, a formal renal impairment study would not be conducted. However, the eligibility criteria of Trial 0039 were extended to include patients with moderate renal impairment in an attempt to assess the effect of renal impairment using a population pharmacokinetic analysis approach.

The drug interaction package consists of the following studies:

18391L/0027: A randomized, open-label, 2-way crossover, Phase I trial to assess the effect of itraconazole, a CYP3A4 inhibitor, on the pharmacokinetics of ZD1839 in healthy male volunteers.

18391L/0030: A randomized, open-label, 2-way crossover, Phase I trial to assess the effect of rifampicin on the pharmacokinetics of a single oral dose of ZD1839 in healthy male volunteers.

18391L/0038: An open Phase I study to assess the inhibitory effect of ZD1839 (IRESSA) on CYP2D6, by comparing the pharmacokinetics of metoprolol (a CYP2D6 substrate), in the presence and absence of ZD1839, in patients with solid tumors.

18391L/0051: A randomized, open-label, crossover, Phase I study to assess the effect of itraconazole, a CYP3A4 inhibitor, on the pharmacokinetics of ZD1839 at doses of 250 and 500 mg in healthy male volunteers

The plan to characterize and quantify ZD1839 metabolites was accepted

A study to assess the effect of hepatic impairment of the pharmacokinetics of ZD1839 is underway (1 8391L/0032) but will not be completed in time for the submission of this NDA.

The plan for population pharmacokinetic analysis was accepted. It was agreed that population PK document will be a stand-alone report and will not be required for the submission of this NDA.

1.3.1 Protocol Amendments - Trial 39

Amendment 1: submitted on 09/19/00

- Inclusion criteria and statistical changes:
- Description of prior chemotherapy regimens and failure of these regimens modified

- Classification at randomization based on prior taxane use removed
- Prior radiation therapy to treat bone metastases or spinal cord compression was
- allowed if completed before Day 1
- Enrollment goal (number of patients) increased
- Clarified symptom improvement rate as a primary end point
- Visit window changed from ±3 to ±5 days of the scheduled date
- Response Evaluation Committee (REQ) to review films only from patients
- having complete or partial tumor response or stable disease
- Safety assessment requirements modified.

Amendment 2: submitted on 01/15/01

- Definitions of required radiographic assessments modified & Biphosphonate therapy allowed to continue for patients receiving therapy at trial entry
- Disease progression on prior chemotherapy clanified
- Screening FACT-L forms to be reviewed for completeness by site staff and sent to
- Astra-Zeneca to determine eligibility (based on LCS score)

Amendment 3: submitted on 01/15/01

- Changes in exclusion criteria:
- Revised criterion for creatinine to be based on creatinine clearance <30 rather than serum creatinine >1.5 times the upper limit of normal
- Added criterion for previous malignancy within 5 years that could confound diagnosis/staging of NSCLC
- Definitions and reporting of AEs modified
- Window of screening FACT-L assessment increased to within 14 days before randomization

Amendment 4: submitted on 08/02/01

- Deleted description of power considerations in statistical comparison of ZD1839 doses
- Clarification to allow radiation therapy to the brain before Day 1
- Reworded criterion to reduce the waiting period after treatment of CNS metastases
- Guideline for dispersing whole ZD1839 tablets added
- Added explanation regarding ZD1839 administration between closure of Trial 18391L/0039 and patient enrollment into Trial 18391L/0026
- Section 5.5 added: Unblinding
- Clarified that patients taking steroids for reasons other than skin toxicity at trial entry may continue treatment
- Stated that partial or complete response had to be confirmed by a repeat tumor assessment 28 days after the response was first observed
- Clarified that any clinically significant CTC Grade 1 or 2 hematology or biochemistry laboratory values considered not due to tumor progression should be reported as an AE
- Redefined the secondary efficacy populations to be included in analyses

- Removed presentation of results by perforinance status and number of prior chemotherapy regimens
- Definition of FACT-L best response reworded
- Correction made to description of validated scoring algorithm for the FACT-L if data are missing
- Definition of overall symptom improvement modified

1.3.2 Sponsor-FDA Summary of Agreements

It is clear from review of FDA comments to sponsor questions (Facsimile 8/11/00, reiterated in facsimile 9/8/00) that all patients enrolled into trial 39 must have documented progression while receiving a docetaxel-containing regimen and a platinum-containing regimen. Exposure to paclitaxel but not docetaxel is not acceptable. Sponsor response to the facsimile of 8/11/00 suggested that prior regimen failure should include progression or intolerance. The FDA agreed and stated "Patients must have received prior treatment with at least two chemotherapy regimens which are docetaxel- and platinum-based (platinum and docetaxel need not be given concurrently). Prior regimens must have failed the patient because of progression or toxicity". Sponsor agreed (8/16/00).

From the standpoint of accelerated approval this was an important agreement. There is no available therapy for third-line treatment for advanced/metastatic NSCLC patients. There are approved treatment regimens for first-line (cisplatin regimens) and second-line (docetaxel) treatment.

Quality of life evaluation was initially considered to be exploratory (1/10/00). The 8/11/00 meeting minutes stated, however, that quality of life is acceptable as a "co-primary" endpoint. "However, it is your task to demonstrate that the symptom findings are credible in a single arm study and are clinically significant. Correlation with objective response may be helpful in this regard".

It was also agreed that the intent to treat population should serve as the primary analysis population, rather than evaluable patients.

1.4 Other Relevant Information

1.4.1 Scientific Rationale

Non-small cell lung cancer (NSCLC) was selected as the initial therapeutic target for ZD1839 because the majority of these tumors overexpress EGFR. Further, phase I clinical studies with ZD1839 provided evidence of antitumor activity in patients with NSCLC. The later studies, together with published studies demonstrating the clinical efficacy of specific, antibody-mediated blockade of erbB2 in patients with breast cancer, provided "proof of principal" that the erbB/HER proteins are important targets for cancer therapy.

1.4.2 Overview of existing treatments for non-small lung cancer

Lung cancer is the most common adult malignancy and accounts for 30% of cancer related deaths in men and 25% of cancer related deaths in women. In the year 2001, an estimated 169,500 patients will be diagnosed with lung cancer in the United States and 157,000 will die (American Cancer Society 2001). Approximately three-quarters of these patients will have NSCLC of whom most will have locally advanced or metastatic disease at diagnosis.

Cytotoxic chemotherapy drugs used to treat good performance patients with newly diagnosed and recurrent advanced NSCLC includes both cisplatin and carboplatin, vinorelbine, paclitaxel, docetaxel and gemcitabine. Three cisplatin-containing doublets have been FDA approved for first-line treatment based on increased survival. A meta-analysis demonstrated that median survival was improved by approximately 6 weeks in patients treated with combination chemotherapy when compared with patients treated with supportive care alone (Non-small Cell Lung Cancer Collaborative Group 1995).

Following inevitable first progression or recurrence, the only therapeutic option is additional chemotherapy. In the second-line setting, 2 randomized Phase III trials report that the median survival with docetaxel was significantly better than the supportive care arm. Docetaxel 75 mg/m2 response rates were 5.5% and 6.7%, respectively.

In addition to limited effectiveness, the use of chemotherapy for palliative treatment of advanced, recurrent NSCLC has limitations due to well-known toxicities. Chemotherapy frequently causes marrow toxicity with associated potentially life-threatening infectious and bleeding complications. Many of the chemotherapy agents used to treat non-small cell lung cancer are associated with peripheral neuropathy. One of the consequences of chemotherapy-induced toxicity is that it can be self-limiting, thus potentially compromising efficacy.

2. Clinically Relevant Findings From Chemistry, Animal Pharmacology And Toxicology, Biopharmaceutics, And Statistics

2.1 ZD1839 Preclinical Antitumor Activity

The antitumor activity of ZD1839 was demonstrated in tests with a range of xenografts derived from different human tissues. ZD1839 was particularly effective against human (vulval) squamous carcinoma-derived cell line A431, which overexpresses EGFR. ZD1839 inhibited the growth of A431 xenografts in a dose-dependent manner and complete inhibition was observed in animals receiving a daily oral dose of 200 mg/kg ZDI 839. Long term treatment (3 to 4 months) completely suppressed A431 tumor growth, and withdrawal of drug treatment allowed tumor growth to resume. When ZD1839 treatment was applied to large, well-established A431-derived tumors, rapid tumor regression was observed, which was sustained for the duration of drug treatment. Tumors re-grew when drug treatment was withdrawn. Thus ZD1839 has a cytostatic effect on tumor cell growth,

stressing the importance of continuous drug treatment to maintain antitumor activity. No evidence for the development of drug resistance emerged, since no A431tumor re-grew during ZD1839 treatment.

2.2 Preclinical evaluation of combinations of ZD1839 with other antitumor agents

The antiproliferative activity of ZDI839, alone or in combination with cytotoxic drugs with different mechanisms of action, was investigated in human ovarian (OVCAR-3), breast (MCF-10A ras; ZR-75-1) and colon (GEO) cancer cell lines, which express EGFR and TGFa. ZD1839 inhibited colony forming ability in a concentration-dependent manner through cytostatic antiproliferative and pro-apoptotic mechanisms. Combining ZD1839 with platins (cisplatin, oxaliplatin, carboplatin), taxanes (paclitaxel, docetaxel), topoisomerase inhibitors (doxorubicin, etoposide, topotecan) or the antimetabolite raltitrexed, markedly enhanced the apoptotic cell death induced by single agent treatment. In studies with colon cancer (GEO) xenografts combined treatment with ZD1839 and cytotoxic agents produced tumor growth arrest and extended the survival of tumor bearing animals. In contrast, combination with gemcitabine had no effect on the latter's cytotoxic activity, and combination with vinorelbine was poorly tolerated.

2.3 ZD1839 Metabolism

Studies of the metabolism of [14C]-ZD1839 were conducted with rat, dog and human hepatocytes, which showed that the compound was metabolised quite extensively in all three species. Using human hepatic microsomes ZD1839 oxidative metabolism was catalysed almost exclusively by CYP3A4. Thus concomitant administration of inducers and inhibitors of CYP3A4 could potentially alter ZD1839 clearance in man. ZD1839 has no obvious enzyme inducing potential and is considered unlikely to produce clinically significant drug interactions due to induction or inhibition of P450 dependent metabolism of coadministered compounds.

The potential contribution of five ZD1839 metabolites identified in humans, to the pharmacological activity of ZD1839, was assessed by measurement of their *in vitro* kinase and cell growth inhibitory activity. Each of the five known metabolites demonstrated potent and selective EGFR kinase inhibition, similar to that of ZD1839. However, when tested for their capacity to inhibit EGF-stimulated cell growth, all of the metabolites were less potent than ZD1839. For example, the major human metabolites M523595 and M537194 were 14- and 7-fold, respectively, less potent than ZD1839. This modest level of activity in cells suggests that the metabolites are unlikely to contribute in a significant manner to the pharmacological activity of ZD1839.

2.4 Toxicology

2.4.1 Single dose toxicity

Following a single oral dose of ZD1839 at 2000 mg/kg to rats, there was a 5 day interval prior to the onset of abnormal signs. All animals showed adverse signs, leading to 4 premature deaths in females. The cause of death of 1 of these 4 decedents was a perforated duodenal ulcer. Other compound-related findings were present in tissues of these animals, including the kidneys, liver, skin and upper gastrointestinal tract. No abnormalities were seen in mice given the same oral dose nor in rats and mice at the maximum achievable dose of 20 mg/kg by the intravenous route. Single oral doses of up to 1000 mg/kg to dogs produced no deaths, but caused adverse effects that had a rapid onset, but were reversible. These effects comprised emesis, diarrhea, loss of skin tone, reduced blood pressure, reduced appetite, loss of body weight and increased plasma ALT, AST and ALP activities.

2.4.2 Repeat dose toxicity

The no effect dose level after administration of ZD1839 to rats and dogs for up to 1 month was 2 mg/kg/day. A dose of 10 mg/kg/day showed only minor changes in red blood cell parameters, plasma protein, and albumin in the 1 month dog study and no adverse effects in the 1 month rat study. A dose of 40 mg/kg/day in the rat for a month, produced reversible increases in plasma ALT and AST levels, but with no pathological correlate. There were histopathological changes in the ovaries of rats (reduced corpora lutea) and in the eyes (corneal epithelial atrophy), kidneys (papillary necrosis), and skin of both rats and dogs, all of which showed signs of partial or full reversibility, 4 weeks after drug withdrawal. These changes were attributed to the pharmacological effects of ZD1839. Reversible prolonged PR intervals, with large variations between individual measurements were recorded for 2 out of 12 dogs at 40 mg/kg/day. In addition, one of these two dogs also showed second degree heart block.

The findings in the 6-month studies were consistent with those detected in the 1 month studies and were similarly attributed to the pharmacological effects of ZD1839. These studies commenced with a high dose of 25 mg/kg/day, however this was not tolerated and the dose level was reduced to 15 mg/kg/day from day 11 in dogs and from week 9 in rats. The no adverse effect dose level, after administration of ZD1839 to rats and dogs for up to 6 months, was 1 mg/kg/day. At 5 mg/kg/day, rats and dogs showed skin lesions and the rats had reversible corneal atrophy of the eyes. These eye effects were more evident in both species at 15 mg/kg/day, but still showed signs of recovery. However, at this dose level in dogs, some areas of opacity developed that did not fully recover during the 12 week withdrawal period. Evidence of an effect on liver function was detected in the rat at 5 mg/kg/day; this was more pronounced in both species at 15 mg/kg/day. In addition, in the rat at this dose, there was hepatocellular necrosis, associated with the increases in plasma liver enzyme levels. A single female dog showed evidence of a reversible effect on P-R interval, similar to that seen in the I month study, at the 15 mg/kg/day dose level.

Multiple dose studies of up to 14 days duration have been conducted in rats and dogs, by the intravenous route. In rats a no effect dose level of 1 mg/kg/day was identified, following once daily bolus intravenous administration of ZD1 839 for 14 days. Compound related effects were seen in the skin, ovary, and uterus of rats receiving 5 or 20 mg/kg/day and were similar to those lesions observed in the oral studies. In dogs bolus intravenous dosing to dogs of ZD1839, at all dose levels, resulted in occasional transient swellings on/around the dosing sites in some animals. The swelling subsided within I to 3 days of first being observed. Swelling was not seen in control animals. The only histopathological changes at the injection sites were consistent with the mechanical trauma of intravenous injection and were essentially similar in all groups, including controls. Minimal folliculitis was found in the eyelid and skin of some dogs, at all dose levels. This effect was consistent with the findings seen in oral toxicity studies.

2.4.3 Genotoxicity

ZD1839 has shown no evidence of genotoxic potential in *in vitro* and *in vivo* assays.

2.4.4 Reproductive and Developmental toxicity

In developmental studies in the rat and rabbit, there was no evidence of teratogenicity in either species. However, at maternally toxic doses in the rabbit, there was fetotoxicity (reduced fetal weights). In the rat pre- post-natal development studies, significant pup mortality in the neonatal period was seen at 20 mg/kg/day (a maternally toxic dose). The no effect dose levels for the developmental and pre and post natal development studies were 5 mg/kg/day and 1 mg/kg/day, respectively. The rat fertility studies showed an effect on ovulation, with reduced fertility at 20 mg/kg/day, with no effects being seen at a dose of 10 mg/kg/day.

When 14C-ZD1839 was dosed orally to pregnant rats and rabbits, radioactivity was found in maternal blood and fetal tissues demonstrating trans-placental transfer of drug-related material. Similarly, in lactating rats dosed with 14C-ZD1839, concentrations of radioactivity in milk were 11 to 19 times higher than those in blood, with ZD1839 accounting for the majority of the radioactivity.

2.4.5 Significant findings by organ system

Ovary: The decreases in ovarian weights, in rats receiving ZD1839 at 40 mg/kg/day in the 1 month study and 15/25 mg/kg/day in the 6 month study, were associated with a reduction in the numbers of corpora lutea. This effect was fully reversed at the end of the withdrawal period. Furthermore, there was evidence of reduced female fertility in the rat at 20 mg/kg/day.

Eye: In the 1 month studies in both rats and dogs, there was evidence for an effect in the eye, detected as corneal epithelial atrophy. This effect had fully reversed at the end of the withdrawal period, although in the dog there was still residual corneal translucency visible ophthalmologically. In the 6 month studies, similar changes were found; in the dog, at the

highest dose tested (25/15 mg/kg/day), the corneal translucencies progressed to corneal opacities, which did not reverse during the withdrawal period. When measured in the dog, there were no changes in tear production rates and the corneal changes were readily identifiable at ophthalmological examination.

Skin: Changes were seen in the skin of rats (inflammatory changes in eyelids, muzzle and inguinal regions) and dogs (inflammatory changes in eyelid region, degenerative changes in hair shafts), which were reversing or had fully reversed by the end of the withdrawal period. Increased white blood cell counts and decreased red blood cell parameters also were seen in a number of the rat and dog studies and were considered to be a sequel to chronic inflammatory skin lesions.

Kidney: In the 1 month studies, renal papillary necrosis was seen in rats and in one dog given ZD1839 at 40 mg/kg/day. This finding was also seen in the 6 month studies, but only at the top dose levels (rats, 15 mg/kg/day; dogs, 25 mg/kg/day (subsequently reduced to 15 mg/kg/day) in a single decedent female). At the end of the withdrawal period in rats, the sequelae of papillary necrosis were observed

Liver: In the rat 6 month study, hepatocellular necrosis and eosinophilic sinusoidal macrophage infiltration were observed with ZD1839 at doses of 5 and 25/15 mg/kg/day. These histopathological changes in rats were clearly associated with increases in plasma liver enzymes (ALP, ALT and AST). Elevated plasma liver enzymes (AST and ALT) were also detected, but no morphological changes were observed in the top dose group (40 mg/kg/day) of the rat 1 month study. No increases in liver enzymes or liver histopathology were observed in dogs.

Gastrointestinal tract: Villous stunting and ulceration of the gastrointestinal tract were observed after administration of single 2000 mg/kg doses of ZD1839 to rats, and villous atrophy/erosions were observed in the 50 and 125 mg/kg/day dose groups in a rat 14 day study. Loose feces were observed in females, on at least one occasion, in the 50 mg/kg/day dose group in the 14 day study. There were no salient findings in the gastrointestinal tract of rats in the 1 and 6 month studies (top doses were 40 and 25/15 mg/kg/day, respectively). Loose feces were recorded in dogs in the 14 day, 1 month, and 6 month studies, with no associated histopathological correlate.
Heart: The lengthened PR intervals, with large variations between individual measurements in 2 out of 12 dogs and the second degree heart block (week 4, ZD1839 40 mg/kg/day) in one of these two dogs also showed that ZD1839 can impair atrioventricular conduction. There was also evidence for a similar effect, in a single animal, in the 6 month study at the top dose level of 15/25 mg/kg/day.

3. Human Pharmacokinetics

A summary of pharmacokinetic conclusions regarding ZD1839 is listed below:

- The iv pharmacokinetics of ZD1839 in cancer patients indicate that it is extensively distributed out of the blood, has relatively high clearance, and has a mean elimination half-life of around 48 h.

- Following oral administration, absorption of ZD1839 is moderately slow, with maximum plasma concentrations typically observed between 3 and 7 h post-dose. The decline in plasma concentrations beyond the peak is biphasic, as would be expected for a drug with extensive distribution, and the mean terminal half-life following oral dosing to cancer patients is of the order of 41 h.

- The oral bioavailability of ZDl 839 is approximately 60% in both healthy volunteers and in patients with advanced solid tumors.

- Within a group of healthy volunteers given the same single dose of ZD1839, the exposures achieved are variable (AUC values typically cover a 20-fold range).

- Within a group of patients given the same single dose of ZD1839, the exposures achieved are variable (AUC values typically cover an 8-fold range).

- Exposure to ZD1839 increases proportionally with dose over the dose range 50 to 250 mg.

- A sustained elevation of gastric pH will result in a reduction in the relative bioavailability of the ZD1839 250 mg tablet of the order of 47%. This reduction in relative bioavailability may be of clinical relevance.

- Multiple daily oral administration of ZD1839 to cancer patients typically results in 2- to 8-fold accumulation, which is consistent with the terminal half-life.

- Steady state plasma concentrations of ZD1839 are achieved within 7 to 10 days of the start of dosing, but may be attained more rapidly by use of a loading dose on Day 1.

- Following once-daily administration, plasma concentrations of ZD1839 across the dosing interval are maintained within a 2- to 3-fold range within individuals.

- In cancer patients within a dose group, measures of steady state exposure (Cmin) to ZD1839 between individuals span up to a 16-fold range of values.

- Within an individual, measures of steady state exposure (Cmin) to ZDI839 span a range of approximately 1- to 3-fold in cancer patients.

- The pharmacokinetics of ZD1839 appear to be independent of the body weight or gender of the subject. However, a weak relationship between plasma clearance and age was seen. A fuller, and more relevant, investigation in cancer patients of the effect on ZD1839 exposure of a range of demographic variables is being conducted on the pooled plasma concentration data obtained from the 2 monotherapy efficacy trials.

- There was no evidence of any ethnic difference in the pharmacokinetics of ZD1839 between Japanese and non-Japanese patients.
- Data are not yet available to assess the impact of impaired hepatic function on exposure to ZD1839.
- The impact of impaired renal function on exposure to ZD1839 is being assessed as part of an ongoing population analysis which is not reported as part of this summary document.
- Most of the radiolabeled ZD1839 dose was excreted in the feces, as parent compound plus metabolites. Less than 4% of the dose was recovered in the urine.
- At least 3 sites of biotransformation have been identified on ZD1839, resulting in the production of 5 identified circulating metabolites, one of which is present at concentrations similar to those of parent compound. None of the identified metabolites is thought to contribute significantly to the overall pharmacological activity of ZD1839.
- ZD1839 does not induce any major cytochrome P450 enzymes.
- The major cytochrome P450 enzyme believed to be involved in the metabolism of ZD1839 is CYP3A4.
- [redacted]

4. Description of Clinical Data and Sources

4.1 Overall Data

NDA 21-399 contains the primary data from two randomized, double-blind, parallel-group, Phase II, multicenter trial of two doses of ZD1839 (Iressa) in patients with advanced/metastatic NSCLC. One trial (Trial 39) includes patients who have previously received at least two chemotherapy regimens that contained platinum and docetaxel given concurrently or as separate treatment regimens (third-line indication). This trial addresses an unmet need. The second trial (Trial 16) includes patients who have failed one or two previous chemotherapy regimens; at least one having contained platinum (primarily second-line indication for which docetaxel is approved). Approximately 50% of patients enrolled in Trial 16 were Japanese. The primary objective of both trials was to evaluate objective tumor response rate and symptom improvement rate with ZD1839 at oral doses of 250 and 500 mg daily. For both trials accrual began in the fall of 2000 and was completed in early 2001.

4.2 Table Listing the Clinical Trials

Table 1: Differences in study populations in pivotal Trial 39 and supportive Trial 16

Trial 39	Trial 16
At least 2 chemotherapy regimens	One or a maximum of 2 chemotherapy regimens
Prior platinum and docetaxel, given concurrently or sequentially	Prior platinum
Prior regimens must have failed due to either unacceptable toxicity or progression while on therapy.	Considered recurrent or refractory
If PD, last dose of chemotherapy within 90 days prior to trial entry	
Symptomatic at trial entry based upon an LCS score of ≤24 a; FACT-L required for randomization	
If treated CNS metastases, patients allowed to: enter 1 week post-completion of definitive treatment (if without neurological deficits), or enter 2 weeks (if stable or improving neurological deficits)	Patients allowed if CNS metastases were clinically and radiologically stable ≥ 2 months prior to entry
Patients with another malignancy within past 5 years able to confound diagnosis and/or staging of NSCLC were excluded. Curatively-treated cervical cancer or non-melanotic skin cancer eligible	
	100 Japanese patients and 100 non-Japanese patients required

a Asymptomatic score is 28.

4.3 Postmarketing Experience

None

4.4 Literature Review

The sponsor submitted an extensive literature list. The reviewer was familiar with most of the clinical data included in those publications.

5. Clinical Review Methods

5.1 How the Review was Conducted

Efficacy and safety review is based on electronic CRT's and hard copy data submitted by the sponsor concerning studies 39 and 16. Additional safety data concerning ZD1839 came from Trials 0005, V-15-11, 0011 and 0012.

5.2 Overview of Materials Consulted in Review

The following materials were reviewed

- Protocols and protocol amendments
- Regulatory history
- Electronic and paper NDA submission
- Relevant published literature
- Digitized radiographs from responding patients

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

Queries of electronic data performed by the FDA reviewer were compared to the sponsor report. Any discrepancies in results prompted a communication to the sponsor aimed at discovering the cause of the discrepancy. All discrepancies, resolved and unresolved, are indicated in the FDA review section of this document.

Tumor measurements and CT-scans from responding patients were independently analyzed by FDA review. Response durations were also confirmed.

Quality of life data obtained from study patients was compared to performance status ratings done by health care professionals. Because performance status is the most important prognostic factor for advanced/metastatic NSCLC patients it was hoped to expore possible correlations between the evaluations.

The FDA also performed an exploratory analysis to determine whether treatment with ZD1839 treatment resulted in improvement in shortness of breath and cough, two common lung cancer symptoms. A positive result of this analysis required a two-point improvement in the specific symptom lasting at least 4 weeks. Because concomitant medication may have contributed to, or have been totally responsible for, any improvement the medication that patients were receiving at the time improvement was noted was reviewed. Classes of drugs considered candidates to improve shortness of breath included narcotics,

bronchodilators, antidepressants/anxiolytics, oxygen, prednisone, and transfusions/epoetin. Classes of drugs considered to improve cough included the above list, minus transfusions/epoetin, plus antibiotics and cough suppressant syrups.To be counted the concomitant medication had to have been started no earlier than the onset of treatment.

5.4 Were Trials Conducted in Accordance with Accepted Ethical Standards

Studies were conducted in accordance with the Declaration of Helsinki, 21 CFR 312 and 314, Directive 91/507/EEC of the European community, and ICH Harmonized Tripartite Guidelines for Good Clinical Practice. The ptrotocol, amendments and study reports were reviewed by IRB's. Written informed consent was required of all study patients.

5.5 Evaluation of Financial Disclosure

- The sponsor certified that no financial arrangement existed with the study clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. Each clinical investigator was also required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor. No investigator disclosed any such interests. Further, no listed investigator was the recipient of significant payments of other sorts.
- Further, participating clinical investigators did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study; had no proprietary interest in this product or significant equity interest in the sponsor of the covered study; and was not the recipient of significant payments of other sorts.
- Further, the sponsor certifies to have acted with due diligence to obtain from the clinical investigators the financial information required and that it was not possible to do so. The relative number of non-responses was small and, in the opinion of the reviewer, extremely unlikely to affect study results.

6 Integrated Review of Efficacy

6.1 Brief Statement of Conclusions

6.1.1 Study 39 - Sponsor's analysis

In study 39 patients with locally advanced or metastatic NSCLC who had previously received and failed at least 2 prior chemotherapy regimens containing platinum and docetaxel therapy, dosing with 250-mg/day or 500-mg/day ZD1839 demonstrated objective tumor response rates of 11.8% and 8.8%, respectively and disease-related symptom improvement rates of 43.1% and 35.1%, respectively. Median progression-free survival times were 59 days and 60 days, respectively. Median survival rates between the 2 dose groups were 185 days for the 250-mg/day group compared to 183 days for the 500-mg/day group

6.1.2 Study 39 - FDA Analysis

FDA agrees with the response rate reported by the sponsor, i.e. 22 partial responses among 216 patients (10.2%, 95% CI 6.5%, 15%). FDA analysis indicated, however, that only 139 of the 216 patients were actually refractory/intolerant to both a platinum drug and to docetaxel. A second concern was that an additional 32 patients were declared to be refractory to therapy within 30 days of starting that therapy. If these individuals are also considered ineligible this would bring the total eligible population to 107 patients. While exclusion of ineligible patients does not appreciably change the overall response rate it does decrease the lower bound of the 95% CI to about 5%.

As might be expected, in a study that is enrolling locally advanced or metastatic NSCLC patients who have failed platinum, docetaxel and other chemotherapy and who still have a performance status of 0 to 2, the patients in this study are not typical of a population of newly diagnosed NSCLC patients of similar stage and performance status. The latter population might be expected to have a median survival of 6 months (stage IV) to 18 months (stage III). Patients in trial 39 had a median time from diagnosis to randomization of 19 months (range 1 to 197 months) and had received a median of 3 prior chemotherapy regimens (range 1 to 6). The 22 ZD1839 responding patients (13 stage IV at diagnosis, 7 stage III) had median time from diagnosis to randomization of 18.5 months (range 8 months to 52 months). Also striking was the fact that 18 of the 22 responders were female and that 19 of the 22 responders had an adenocarcinoma. Adenocarcinoma has the slowest tumor doubling time of all lung cancer histologies. Demography and disease status of study patients is found in Tables 3 and 4, pages 43-44.

6.1.3 Study 16 - Sponsor's analysis

In patients with locally advanced or metastatic NSCLC who had previously received at least one chemotherapy regimen containing platinum, dosing with 250-mg/day or 500-mg/day ZD1839 resulted in: 1) objective tumor response rates of 18.4% and 19.0%, respectively; 2) disease-related symptom improvement rates of 40.3% and 37.0%, respectively; 3) disease control rates of 54.4% and 51.4%, respectively; 4) QOL improvement rates for TOI of 20.9% and 17.8%, and for FACT-L of 23.9% and 21.9%, respectively median progression-free survival times of 83 days and 85 days, respectively.

Significant differences were observed between Japanese and non-Japanese patients with respect to tumor response, disease control, progression-free survival, and overall survival. No correlation between demographic/pathophysiological factors (including ethnicity) and ZD1839 exposure were identified.

6.1.4 Study 16 - FDA Analysis

Trial 16 is a supporting trial primarily including second-line patients. As in trial 39 eligibility issues were identified by FDA. By FDA analysis 136 of the 209 patients (65.1%) in the ITT population had not progressed during or after prior chemotherapy treatment. The

median/mean time from diagnosis to randomization was 12.1/15.9 months (range 0.1 to 125 months). There was 1 complete response and 38 partial responses. Eleven of 102 Caucasian patients were responders compared to 28 of 102 Japanese patients. Thirty-four responders had an adenocarcinoma and 1 had a mixed adenocarcinoma-squamous cell carcinoma. Seventy-four percent of responders had not progressed on prior chemotherapy. The majority of responding patients had lung tumors only or lung plus nodal involvement. Progression free survival and overall survival was comparable to the sponsor's estimates. Demography and disease status of study patients is found in Tables 24 and 25, pages 66-67.

6.2 General Approach to Review of Drug Efficacy

The efficacy database consists of two phase II, open label trials in patients with locally advanced or metastatic NSCLC, who had previously received and failed at least 2 prior chemotherapy regimens containing platinum and docetaxel therapy or who had previously received at least one chemotherapy regimen containing platinum, who were randomized to ZD1839 250-mg/day or 500-mg/day.

6.3 Detailed Review of Trials by Indication per Sponsor

6.3.1 Investigators

Investigator Study:Site
Kathy Albain MD 18391 L/0039:2251

Loyola University Medical Center
2160 S. I st Avenue Room 109,
Maywood EL60153 USA
Dr J-P Armand 18391L/0012:008
Department of Medical Oncology
Institute Gustave Roussy
Rue Camille Desmoulins
Villejuif9485 France
Dr J Baselga, 18391L/0012:005
Department of Oncology
Vall d'Hebron General Hospital
Paseo Val] dHebron 119-129
08035 Barcelona Spain
Dr J Baselga 18391L/0016:005
Vall d'Hebron General Hospital

Paseo Vall d'Hebron 119-129
08035 Barcelona Spain
Dr R Basser 18391L/0016:109
Western Hospital
Gordon Street
Footscray
Melbourne VIC 3011 Australia
Chandra P Belani MD 18391L/0039
University of Pittsburgh Cancer
Institute
200 Lothrop Street
Pittsburgh PA 15213-2546 USA
Dr T Bjork 18391L/0012:010
Department of Urology

Malmo University Hospital
105 02 Malmo Sweden
Julie R Brahmer MD 18391L/0039:2256
Hopkins Bunting-Blaustein
Cancer Research
Building G94 1650 Orleans Street
Baltimore MD 21231 - 1000 USA
Dr R Callaghan 18391L/00 16:251
I Hopelands Court
Hopelands Road
4001 Overport South Africa

Professor A H Calvert
18391L/0012:002
Department of Oncology
Northern Centre for Cancer
Treatment
Newcastle General
Westgate Road
Newcastle upon Tyne NE4 6BE UK
Dr S Casinu. 18391L/0016:704
Oncologia Medica Azienda
Ospedaliera. di Panna
Viale Gramsci 14
43 100 Parma Italy
John Cole MD 18391L/0039:2059
Oschner Cancer Institute
New Orleans LA 70121-2483 USA
Jeffrey Crawford MD
18391L/0039:2072
Duke University Medical Center
Room 25178
Morris Building Box 3198
Durham NC 277 10 USA
Dr L Dirix 18391L/00 16:205
AZ St Augustinus
Oncologisch Centrum
Oosterveldlaan 24
B-26 10 Wilrijk Belgium
Dr J E Dixon 18391L/0003:002
Inveresk Research International Ltd,
Tranent,
Edinburgh EH33 2NE, UK
Professor J Y Douillard
18391L/0016:415
CRLCC Rene Gauducheau.
Bd Jacques Monod
44805 Saint-Herblain France
Dr D Ferry 18391L/0005:004
CRC Trials Unit
Clinical Research Block
Queen Elizabeth Hospital
Edgbaston
Birmingham B 15 2TT UK
David R Gandara 18391L/0039:2252
University of California
Davis Cancer Center
4501 X Street
Sacramento CA 95817-2229 USA

Dr U Gatzemeier 18391L/0016:501
Krankenhaus Grosshandsdorf
Onkologischer Schwerpunkt
Wohrendamm, 80
22927 Grosshansdorf Germany
Hal Gerstein MD 18391L/0039:2274
Cancer Research of Long Island
170 Great Neck Road Suite 100
Great Neck NY 11201 USA
Professor G Giaccone 18391L/0016:601
Academisch Ziekenhuis Vrije
Universiteit Afdeling
De Boelelaan 1117
1081 HV.Amsterdam The Netherlands

Dr L Gianni 18391L/0012:007
Department of Oncology
Istituto Nazionale Tumon*
Via Venezian
120 100 Milano MI Italy
John Hamm MD 18391L/0039:2273
Norton Healthcare Inc
Louisville Oncology
315 E Broadway 5th Floor
Louisville KY 40202 USA
Lisa Hammond MD 18391L/0039:2010
Cancer Therapy Research Center
7979 Wurzba6h Road Room 271
San Antonio TX 78229 USA
Professor A Harris 18391L/0012:004
ICRF Clinical Oncology Unit
Churchill Hospital
Headington
Oxford OX3 7LJ UK
Dr R Herbst 1839 1 L/001 1:002
University of Texas MD
18391L/0039:2002
Anderson Cancer Center
1515 Holcombe Boulevard, Box 80
Houston TX 77030-4009 USA
Dr T Horai 18391L/0016:818
Japanese Foundation for Cancer
Research
Cancer Institute Hospital
1-37-1 Kami-lkebukuro
Toshima-ku Tokyo Japan
Dr D G Kieback 18391L/0012:006
Department of Obstetrics and
Gynaecology I

Dr F Imamura. 18391L/0016:822
Osaka Medical Centre for Cancer
and Cardiovascular Diseases
1-3-3 Nakarmchi
Higashinarie-ku, Osaka, Japan
Mohammad Jahanzeb MD
18391L/0039:2057
Comprehensive Cancer Center at
Boca Raton
21020 State Road 7
Boca Raton FL 33428 USA
Leonard A Kalman MD
18391L/0039:2085
Oncology Hematology Group of
South Florida
8940 North Kendall Drive Suite 300E
Miami Fl, 33176 USA
Joseph Kash MD 18391L/0039:2271
Edwards Hospital Cancer Center
120 Spalding Drive Suite 400
Naperville IL 60540 USA
Dr N Katakami 18391L/0016:812
Kobe Municipal Central Citizens
Hospital
4-6 Minatoshimanaka-cho
Chuo-ku, Kobe-shi
Hyougo Japan
Professor E Kaukel 18391L/0016:503
Krankenhaus Harburg
Lungenstation
Eissendorfer Pferdeweg 52
21075 Hamburg GenTiany
Professor S Kaye 18391L/0012:001
Beaston Oncology Centre
Western Infirmary
Glasgow G I 16NT UK
Karen Kelly MD 18391L/0039:2253
B171 UCHSC
4200 E 9th Avenue
Denver CO 80262 USA
Professor D Kerr 18391LJO035:001
CRC Institute for Cancer Studies
Queen Elizabeth University Hospital
Trust
Birmingharn, B 15 2TH UK
Dr A Lockton 18391L/0027:001
AstraZeneca Clinical Pharmacology
Unit Nottingham
E Floor South Block
Queen's Medical Centre
Derby Road

University Hospital Freiburg
Hugstetter Strasses 55
79106 Freiburg Germany
Dr K Kiura 18391L/0016:803
Okayama University Medical
Department
2-5-1 Shikada-cho
Okayama-shi, Okayama, Japan
Dr M Kris 18391L/0005:002
Memorial Sloan-18391L/0039:2012
Kettering Cancer Center
York Avenue
New York, NY 10021-6007 USA
Dr S Kudou 18391L/0016:815
Osaka Municipal University 1839N-15-
11
Medical Department
1-5-7 Asahi-cho
Abenoku-Ku
Osaka-sh, Osaka, Japan
Dr A Laight 18391L/0030:001
Clinical Pharmacology Unit
18391L/0031:001
AstraZeneca Pharmaceuticals
18391L/0033:001
Mereside 18391L/0034:001
Alderley Park 18391L/0051:001
Macclesfield SKI 0 4TG UK
Dr J L G Larriba 183911/0016:916
Hospital Clinico S Carlos de Madrid
Departmento Oncologia
c) Martin Lagos S/N
28040 Madrid Spain
Corey Langer, MD 18391L/0039:2115
Fox Chase Cancer Center
770 Burholme Avenue
Philadelphia PA 19111-2412 USA
Rogerio Lilenbaum MD
18391L/0039:2102
Comprehensive Cancer Center
Mt Sinai Medical Center
4306 Alton Road
Miami Beach Fl, 33140-2840 USA
Dr K Matsui 18391L/0016:813
Osaka Prefecural Habikino Hospital
3-7-1 Habikino
Habikino-shi
Osaka Japan
Dr. I Meyer 18391L/0028:001
Quintiles GmbH
Geschaftsstelle Freiburg
Nottingham NG7 2LTH UK

Dr P LoRusso 18391L/001 1:003
Harper Hospital at Wayne State
University
3990 John R Street, Room 530
Detroit MI 48201-2097 USA
Stuart Lutzker MD 18391L/0039:2008
Cancer Institute of New Jersey
195 Little Albany Street
New Brunswick NJ 08901-1914 USA
Thoma J Lynch MD 18391L/0039:2028
Massachusette General Hospital

Box 2, 100 Blossom Street
Boston MA 02114 USA
Dr A M Maddox 18391L/00 11:001
University of Arkansas Cancer
Research Center
4301 West Markham, Slot 508
Little Rock AR 72205-7101 USA
Dr A M Maddox 18391L/0039:2101
University of Arkansas Cancer
Research Center
4301 West Markham, Slot 508
Little Rock AR 72205-7101 USA

Professor C Manegold 18391L/0016:504
Thoraxkllnik Heidelberg-Rohrbach
Innere Medizin Hamatologie
Intemistische Onkologie
Amalienstrasses 5
69126 Heidelberg Germany
Dr N Masuda 18391L/0016:813
Osaka Prefecural Habikino Hospital
3-7-1 Habikino
Habikino-shi, Osaka, Japan

Dr K Noda 18391L/0016:804
Kanagawa Prefectural Cancer Centre
1- 1 -2 Nakao
Asahi-ku
Yokoharna-shi
Kanagawa Japan
Dr OM Nwose 183911/0051:001
Clinical Pharmacology Unit

Obere Hardstrasse 8-16
Freiburg-D79114 Germany
Dr B Milleron 18391L/0016:414
Hopital Tenon
Service de Pneumologie
Rue de la Chine
75970 Paris Cedex 20 France
Dr P Mitchell 18391L/001 6:110
Austin & Repatriation Medical
Centre
Cancer Clinical Trials Centre
Studley Road
Heidelberg VIC 3084 Australia
Dr D Moro-Sibilot 18391L/0016:416
Hopital A Michallon
Service de Pneumologie
BP217X
38000 Grenoble France
Dr K Nakagawa
18391L/0016:805
Kinki University Medical 1839N-15-11

Department Hospital
377-2 Oonohigashi
Osakasayama-shi, Osaka Japan

Ronald Natale 18391L/0039:2090
Cedars Sinai Comprehensive Cancer
Center
8700 Beverley Blvd Suite C-2000
Los Angeles CA 90048 USA
Dr.S.Negoro 1839N-15-11
Osaka City General Hospital
Respiratory Tract Internal Medicine
Dr Y Nishiwaki
18391L/0016:821
National Cancer Centre East Hospital
6-5-1 Kashiwanoha
Kashiwa-shi Chiba Japan
Dr D Rischin
18391L/0012:011
Division of Haematology 18391L/001
6:111
and Medical Oncology
Peter MacCallum Cancer Institute
St Andrews Place East Melbourne 3002

Dr R Rosell 18391L/0016:908
Hospital Universitario Germans
Trais I Pujol
Departmento Oncologia

AstraZeneca Pharmaceuticals
Mereside, Alderley Park
Macclesfield, Cheshire SKI 0 4TG UK
Timothy Panella MD 18391L/0039:2044
Thompson Cancer Survival Center
Clinical Trials Department
1915 White Avenue
Knoxville TN 37916 USA
Diane Prager MD 18391L/0039:2255
UCLA Medical Center
10945 Le Conte Avenue
Suite 2333 PUVB
Los Angeles CA 90024-2828 USA
Professor J L Pujol 18391L/0016:417
Hopital A de Villeneuve
Service de Pneumologie
371 Avenue du Doyen Giraud
34295 Montpellier Cedex France
Dr.M.Ranson 18391L/0005:003

CRC, Department of Medical
18391L/0012:003
Oncology, 18391L/0035:002
Christie NFIS Trust 18391L/0038:001
Wilinslow Road,
Withington, Manchester M2 9BX. UK

Dr B Rapaport 18391L/0016:257
Medical Oncology Centre of
Rosebank
177 Jan Smuts Avenue
2193 Parktown North South Africa
Dr E Raymond 18391L/0012:008
Department of Medical Oncology

Institute Gustave Roussy
Rue Camille Desmoulins
Villejuif 9485 France
Mansoor Salch MD 18391L/0039:2270

Georgia Cancer Specialist

1872 Montreal Road
Tucker GA 30084 USA

Allen Sandier MD 183911/0039:2011
Vanderbilt University Medical Center
1956 The Vanderbilt Clinical
Hematology and Oncology Dept
Nashville TN 37232-5536 USA

Ctra Del Canyet
SIN Badalona
08915 Barcelona Spain
Dr M Rosenthal 18391L/0016:112
Royal Melbourne Hospital
Grattan Street
Parkville
Melbourne VIC 3050 Australia
Dr M Rothenberg 18391L/001 1:004
Division of Hematology-Oncology
Department of Medicine
1956 The Vanderbilt Clinic
Nashville TN 37232-5536 USA
Dr E Rowinsky 18391L/0005:001
Cancer Therapy & Research Center
7979 Wurzbach Rd
San Antonio TX 78229 USA
Dr E Rubin 18391L/001 1:008
Cancer Institute of New Jersey
195 Little Albany Street
New Brunswick NJ 08901-1914 USA
Dr P Ruff 18391L/0016:258
Johannesburg Hospital
Haematology and Oncology
Department
York Road
2193 Parktown South Aftica
Dr H Saka 18391L/00 16:801
National Nagoya Hospital
4-1-1 Sannomaru
Naka-ku.
Nagoya-shi
Aichi Japan

Dr E Small 18391L/001 1:005
University of California at San
Francisco Comprehensive Cancer
Center
1600 Divisardaro Street 3rd Floor

San Francisco CA94115 USA
Charalampox Spiridonidis
18391L/0039:2107
Oncology Consultants Inc
8100 Ravine's Edge Court Suite 100
Columbus OH 43235 USA

Philip Stella MD 18391L/0039:2236
5301 E Huron Drive
Ann Arbor MI 48106 USA
Dr T Sugiura 18391L/0016:817
Aichi Prefectural Cancer Centre

Dr A Santoro 18391L/0016:712
U 0 Oncologia Medica
ed Ematologia Istituto Clinico
Humanitas
Via Manzoni 58
20089 Rozzano (MI) Italy
Dr T Sawa 183911/0016:820
Gifu Citizens Hospital
7-1 Kashima-cho
Gifu-shi
Gifu Japan
Professor G Scagliotti 18391L/0016:713
Divisione di Pneumologia
Oncologia Azienda
Ospedaliera S Luigi
Regione Gonzole
10043 Orbassano (TO) Italy
Joan Schiller MD 18391L/0039:2064
University of Wisconsin Cancer
Center
600 Highland Avenue Room K 4/636
Madison WI 53792-6164 USA
Arthur Skanin MD 18391L/0039:2201
Dana-Farber Cancer Institute
Lowe Center for Thoracic Oncology
44 Binney Street
Boston MA 02115 USA
Dr C Slabber 18391L/0016:259
Mary Potter Oncology Centre
c/o Totius Street and George Storar
Street
Groenklook
Pretoria South Africa
M Roy Thomas MD 18391L/0039:2026
Mid Dakota Clinic
401 N 9th Street
Bismarck ND 58501 USA
Professor J Vansteenkiste
18391UO016:207
UZ Gasthuisberg Longziekten
Respiratoire Oncologie

Herestraat 49
B-3000 Leuven Belgium

Dr K Watanabe 18391L/0016:808
Yokohama Citizens Hospital
56 Okasawa-cho
Hodogaya-ku
Yokohama-shl
Kanagawa Japan

1-1 Kanokoden
Chikusa-ku
Nagoya-shi
AichiJapan
Dr M Takada 18391L/0016:811
Rinku. General Medical Centre
Municipal Izumisano Hospital
2-23 Rinku Oral Kita
Izumisano-shi
Osaka Japan
Dr I Takata 18391L/0016:802
National Hospital Shikoku
Cancer Centre
13 Horinouchi
Matsuyama-shi
Ehime Japan
Dr K Takeda 18391L/0016:807
Osaka Municipal General Medical
Centre
2-13-22 Hon-street
Miyakojima
Miyakojima-ku
Osaka-shi
Osaka Japan

Dr T Tamura 18391L/0016:819
National Cancer Centre 1839N- 15-
11:001
Central Hospital
5-1-1 Tsukiji
Chuo-ku
Tokyo Japan

Professor D Webb 18391L/0001:002
Clinical Research Centre,
Department of Medicine,
The University of Edinburgh,
Western General Hospital,
Edinburgh EI-14 2XU UK
Dr C H Wilder-Smith 18391L/0036:001
Gastroenterology Group Practice
Physiology and Nociception
Research Group
University of Berne
Bubenbergplatz 11
CH-3011 Berne Switzerland
Dr S Yano 18391L/0016:814
Tokushima University Medical
Department
2-50-1 Kuramoto-cho
Tokushima-shi
Tokushima Japan
Dr R A Yates 18391L/0001:001
Clinical Pharmacology Unit,
18391L/0002:001 183911/0010:001
Zeneca Pharmaceuticals
18391L/0003:001
Mereside, Alderley Park,
Macclesfield, Cheshire SKI 0 4TG UK
Dr A Yokoyama 183911/0016:800
Niigata Prefecural Cancer Centre

Niigata Hospital
2-15-3 Kawagishi-cho
Niigata-shi, Niigata, Japan

6.3.2 Common Protocol Elements – Trials 39 and 16.

6.3.2.1 Study Objectives

The primary objectives in Trials 39 and 16 were objective tumor response rate of ZD1839 at both 250 mg and 500 mg daily doses, disease-related symptom improvement rate and safety profile characterization of 250 mg and 500 mg daily ZD1839. Secondary objectives were disease control rates (responses + stable disease), progression-free survival and overall survival, time to worsening of symptoms, changes in Quality of Life, and, in trial 16, to evaluate potential differences between Japanese and non-Japanese patients.

6.3.2.2 Eligibility Criteria

Both trials required histologically confirmed advanced NSCLC. Patients had to be at least 18 years old, had to have at least 1 bi-dimensionally measurable lesion with clearly defined

margins or non-measurable but evaluable disease at trial entry, had to be WHO performance status of 0 to 2 and had to provide written consent to participate in the trial. Both trials permitted patients with stable brain metastases to be enrolled.

The 2 trials, however, differed on several key eligibility criteria. These criteria ensured that the patient population in Trial 39 had more advanced and refractory disease, and required presence of disease-related symptoms at baseline in order to assess symptom improvement rates. For trial 39 patients must have failed prior platinum and docetaxel, given concurrently or sequentially. Failure of prior regimens must be due to either unacceptable toxicity or progression while on therapy. If PD, last dose of chemotherapy must be within 90 days prior to trial entry. For trial 16 eligible patients must be recurrent or refractory to one or a maximum of 2 chemotherapy regimens that included prior platinum. Trial 16 required 100 Japanese patients and 100 non-Japanese patients.

6.3.2.3 Schedule of Trial Assessments

The schedule of trial assessments is listed in **Table 2.**

Table 2: Schedule of trial assessments

Event or assessment	Screening		Monthly (every 28 days)		Discontinuation
	Day -14 to 0	-7 to 0	1 14	28/1	
	Visit	1	2	3+	
General events or assessments					
Informed consent	x				
Demography	x				
Medical history and cancer treatments	x				
Concurrent illness/therapy		xa	x	x	x
Physical examination (performance, status, weight and vital signs)		xa	x	x	x
Pregnancy test, if appropriate		x			
Blood sampling for pharmacokinetics analysis			x	x	x
Dispense tablets			x	x	
Efficacy assessments					
Tumor assessment	xb			x	x
Quality of life (FACT-L)	x				x
Lung cancer subscale (LCS) symptom checklistf				Weekly	
EGFR status (recut sections, paraffin embedded tissue block, or slides from diagnosis or later)	x				
Survival				x	x

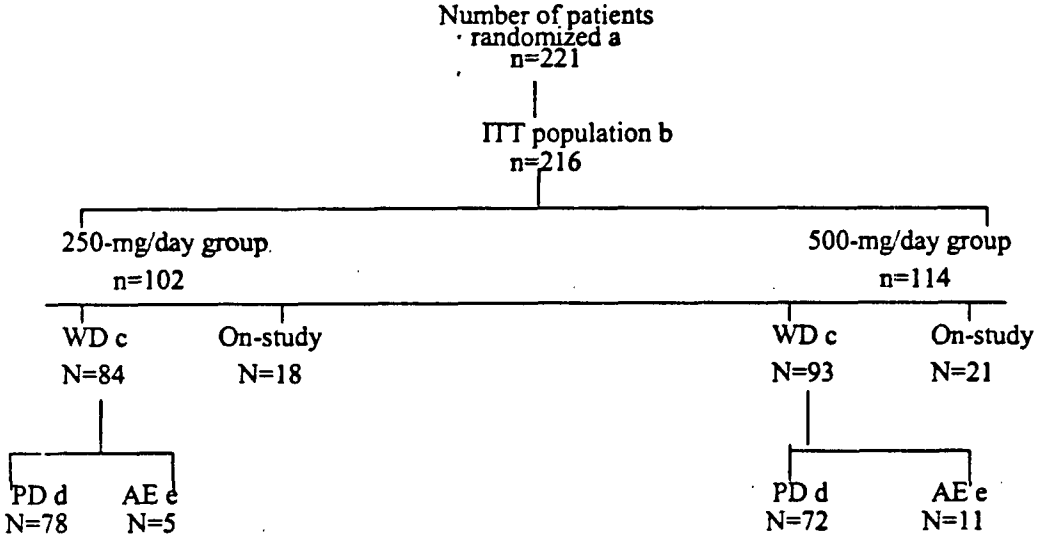
a if a parameter or condition was assessed within 7 days before randomization and findings were consistent with the eligibility criteria, then reassessment on Day 1 was not required.
b Tumor assessment was required within 14 days before randomization, approximately 28 days and 56 days after randomization, and approximately every 8 weeks thereafter.

6.3.3 Pivotal Trial 39 - Patient Population/Demography/ Disease Status/ Prior Cancer Therapy – Sponsor Analysis

Overall, 221 patients from 30 centers in the US were randomized, of whom 216 received trial treatment. Five patients were randomized but did not receive ZD1839 treatment due to either disease progression, a serious adverse event, or screening failure.

Patient populations are summarized in **Figure 3**. Of the 216 patients treated (ITT population), 181 were considered evaluable for the per-protocol (PP) population (ie, had no significant protocol violations or deviations). Patient demography is summarized in **Table 3** while disease status at entry is summarized in **Table 4**.

Figure 3: Trial 39 Study Population



a Patients who signed informed consent to participate in the trial.
b Patients who were randomized and received at least 1 dose of trial drug.
c Number of patients who withdrew from trial
d Number of patients who withdrew from the trial due to progressive disease.
e Number of patients who withdrew from the trial due to an adverse event.

Table 3: Demographic characteristics, ITT population in Trial 39

Characteristic	ZD1839 dose		Total
	250 mg/day	500 mg/day	
	N=102	N= 114	N=216
Age (y)			
Mean (SD)	59.3 (11.0)	60.7 (10.3)	60.0(10.7)
Median	61.0	62.0	61.0
Range	34 to 84	30 to 80	30 to 84
Age distribution (y), n			
18-64	64 (62.7)	66 (57.9)	130 (60.2)
≥65	38 (37.3)	48 (42.1)	86 (39.8)
Sex, n (%)			
Male	60 (58.8)	63 (55.3)	123 (56.9)
Female	42 (41.2)	51 (44.7)	93 (43.1)
Origin, n (%)			
White	93 (91.2)	103 (90.4)	196 (90.7)
Black	3 (2.9)	4 (3.5)	7 (3.2)
Asian a	1 (1.0)	3 (2.6)	4 (1.9)
Hispanic	2 (2.0)	3 (2.6)	5 (2.3)
Other b	3 (2.9)	1 (0.9)	4 (1.9)

a Includes categories of Asian and Oriental. b Includes Hawaiian, Israeli, Taiwanese, and origin unreported (n=1 each).

Table 4: Disease status at entry, ITT population in Trial 39

Characteristic, n (%) of patients	ZD1839 dose		Total
	250 mg/day N=102	500 mg/day N=114	N=216
Disease type			
Measurable	87 (85.3)	103 (90.4)	190 (88.0)
Nonmeasurable and evaluable	15 (14.7)	11 (9.6)	26 (12.0)
WHO performance status			
0	18 (17.6)	15 (13.2)	33 (15.3)
1	64 (62.7)	75 (65.8)	139 (64.4)
2	19 (18.6)	23 (20.2)	42 (19.4)
3	0	1 (0.9)	1 (0.5)
Not recorded	1 (1.0)	0	1 (0.5)
Tumor histology type			
Squamous	14 (13.7)	18 (15.8)	32 (14.8)
Adenocarcinoma	70 (68.6)	73 (64.0)	143 (66.2)
Undifferentiated	9 (8.8)	8 (7.0)	17 (7.9)
Large cell	2 (2.0)	3 (2.6)	5 (2.3)
Squamous and adeno	7 (6.9)	9 (7.9)	16 (7.4)
Not recorded	0	3 (2.6)	3 (1.4)
Current disease status			
Locally advanced	15 (14.7)	9 (7.9)	24 (11. 1)
Metastatic	87 (85.3)	105 (92.1)	192 (88.9)
Sites of metastatic disease			
Adrenal gland	12 (11.8)	15 (13.2)	27 (12.5)
Bone	25 (24.5)	32 (28.1)	57 (26.4)
Brain	19 (18.6)	15 (13.2)	34 (15.7)
Liver	20 (19.6)	31 (27.2)	51 (23.6)
Lung	53 (52.0)	71 (62.3)	124 (57.4)
Lymph nodes	43 (42.2)	53 (46.5)	96 (44.4)
Skin or soft tissue	6 (5.9)	5 (4.4)	11 (5.1)
Other a	11 (10.8)	16 (14.0)	27 (12.5)

a Includes sites of pleural and pericardial effusion.
ITT Intent-to-treat, WHO World Health Organization.

Previous cancer treatment is provided in **Table 5.**

Table 5: Previous cancer treatment, ITT population in Trial 39

Characteristic	ZD1839 dose		Total
	250 mg/day N=102	500 mg/day N=114	N=216
Number of prior chemotherapy regimens, n (%)			
1 a	2(2.0)	0	2 (0.9)
2	41(40.2)	48(42.1)	89 (41.2)
3	31(30.4)	41(36.0)	72 (33.3)
4 or more	28(27.5)	25(21.9)	53 (24.5)
Reason for discontinuation of most recent chemotherapy, n (%)			
Progressive disease	82(80.4)	88(77.2)	170 (78.7)
Unacceptable toxicity	15(14.7)	23(20.2)	38 (17.6)
Completion of therapy b	1 (1.0)	1 (0.9)	2 (0.9)
Other b	4(3.9)	2(1.8)	6 (2.8)
Interval from diagnosis to randomization (months)			
Median/mean	23.8/28.5	16.6/23.7	19.6/26.0
Minimum	1	4	1
Maximum	172	197	197
Prior taxane use, n (%)			
Docetaxel only	22(21.6)	32(28.1)	54 (25.0)
Docetaxel and paclitaxel	79(77.5)	81 (71.1)	160 (74.1)
Paclitaxel only c	1 (1.0)	1 (0.9)	2 (0.9)
Other prior cancer treatment, n			
Radiotherapy	74(72.5)	74(64.9)	148 (68.5)
Surgery	59(57.8)	62(54.4)	121 (56.0)

a Patients who did not receive 2 prior chemotherapy regimens were excluded from the PP population; however, it was determined upon data clarification that 1 of these patients (Patient 2102/0028) did have more than 1 prior regimen. Correction of the start dates of prior chemotherapy could not be made before database lock, however, so the number of prior regimens listed in the database remains 1. The patient was not excluded from the PP population.

b Patients who did not fail prior treatment due to disease progression or unacceptable toxicity were excluded from the PP population.

c Patients who did not receive prior docetaxel treatment were excluded from the PP population.

6.3.3.1 Efficacy results - Objective responses – Sponsor Analysis

Tumor assessments were performed 14 days before the start of treatment (randomization); 28 days and 56 days after randomization, and approximately every 8 weeks thereafter.

Summary data for best tumor response are summarized in **Table 6**. A total of 12 (11.8%; 95% CI: 6.2%, 19.7%) patients showed partial responses in the 250-mg/day group and ten (8.8%; 95% CI: 4.3%, 15.5%) patients showed partial responses in the 500-mg/day group. Patients with stable disease were distributed proportionately between groups with 31 (30.4% of the treatment group) in the 250-mg/day group and 31 (27.2% of the treatment group) in the 500-mg/day group.

Table 6: Summary of objective tumor responses in the ITT population

ZD1839 dose

Parameter	250 mg/day N=102	500 mg/day N=114
Number of patients with tumor response [n,	12(11.8)	10(8.8)
Partial response in measurable disease	9	9
Partial response in non-measurable disease	3	1
Number of patients with SD [n,	31(30.4)	31(27.2)
Number of patients with PD [n,	54(52.9)	59(51.8)

The majority of the objective partial responders with measurable disease (72.2%, 13/18) had total tumor volumes > 10 cm2; only 3 patients had total tumor volumes < 5 cm2 Reductions in tumor size occurred in mainly lung (20 patients), liver (4 patients), lymph nodes (5 patients), but also occurred in adrenal (1 patient), kidney (1 patient), and bone (1 patient). All but 1 patient (95.5%, 21/22) also had disease-related symptoms improvement as measured by the LCS. These disease-related symptom improvements were observed by nearly all patients within 4 weeks of starting treatment.

The majority of patients (72.7%, 16/22) who achieved a response did so by the third (4 patients) or fourth week (12 patients); 3 patients achieved a response by Week 7, 1 by Week 12, and 2 by Week 16..

Baseline characteristics of patients who had a tumor response (PR or PRNM) are presented in **Table 7**.

Table 7: Tumor response rate by baseline characteristics in Trial 39

Characteristic, n (%) of patients	n b	Tumor response a	
		Yes (N=22)	No (N= 194)
Disease type			
Measurable	190	18 (9.5)	172 (88.7)
Non-measurable only	26	4(15.4)	22 (84.6)
Disease status at trial entry			
Locally advanced	24	0	24(100.0)
Metastatic	192	22 (11.5)	170 (88.5)
WHO performance status			
0-1	172	16 (9.3)	156 (90.7)
2	42	6 (14.3)	36 (85.7)
3	1	0	1 (100.0)
Not recorded	1	0	1 (100.0)
Number of prior number of treatments			
1	2	0	2(100.0)
2	89	7(7.9)	82 (92.1)
3	72	7 (9.7)	65 (90.3)
4 or more	53	8 (15.1)	45 (84.9)
Gender			
Female	93	18 (19.4)	75 (80.6)
Male	123	4(3.3)	119(96.7)
Age			
18-64	130	13 (10.0)	117(90.0)
≥65	86	9(10.5)	77 (89.5)
Ethnic origin			
White	196	17 (8.7)	179 (91.3)
Non-white c	20	5 (25.0)	15 (75.0)
Histology			
Squamous	32	2 (6.3)	30 (93.7)
Adenocarcinoma	143	19 (13.3)	124(86.7)
Undifferentiated	17	1 (5.9)	16(94.1)
Large cell	5	0	5 (100.0)
Squamous and adenocarcinoma	16	0	16(100.0)
Not recorded	3	0	3 (100.0)

a Both doses combined.
b Number of total patients in a given category.
c Includes Black, Asian/Oriental, and Hispanic.

Response Duration

The median duration of tumor response, as of 7/23/02, is 7.0 months (95% CI 5.7-8.9 mo, range 3.4-18.6+ mo.) for ZD1839 250 mg. and 5.8 months (95% CI 4.5-11.7, range 4.4-15.6+) months for ZD1819 500 mg/day.

6.3.3.2 Disease-related symptom improvement – Sponsor Analysis

Trial 39 used the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) instrument to assess disease-related symptoms. The maximum or "best" score is 28, which indicates no symptoms; the minimum or "worst" score is 0 indicating that the patient is severely bothered by all 7 symptoms. Patients had to have a LCS score of 24 or less as a eligibility criterion.

Weekly assessments of disease-related symptoms were made. Changes from baseline in the LCS score were assessed at each visit as improved or worsened if the score had shifted at least 2 points in either direction. To be considered as having "disease-related symptom improvement", the patient had to sustain a 2-point or more improvement in their total LCS score for a minimum of 4 weeks without interim worsening to minimize potential for false positive responses.

The overall completion compliance was 84%. There was no apparent difference in compliance between the doses.

LCS baseline characteristics

The baselines distribution of each LCS item by score for all patients is presented in **Table 8**. The median baseline score for LCS was 16.0 and 81 % of the patients had baseline scores less than 20.

Table 8: Disease-related symptom distribution at baseline by score for all patients

Disease-related symptom	N	Baseline score [n(%)] Most Symptomatic 0	1	2	3	No Symptomatic Sx 4
Shortness of breath	216	28 (13.0)	70 (32.4)	62 (28.7)	36 (16.7)	20(9.3)
Coughing	215	32 (14.9)	62 (28.8)	48 (22.3)	42 (19.5)	31(14.4)
Chest tightness	212	13 (6.1)	23 (10.8)	44 (20.8)	66 (31.1)	66(31.1)
Ease of breathing	213	28 (13.1)	37 (17.4)	85 (39.9)	41 (19.2)	22(10.3)
Weight loss	216	10(4.6)	17 (7.9)	42 (19.4)	50 (23.1)	97(44.9)
Clarity of thinking	215	7 (3.3)	6 (2.8)	40 (18.6)	61 (28.4)	101(47.0)
Poor appetite	214	24(11.2)	35 (16.4)	60 (28.0)	53 (24.8)	42 (19.6)

The disease-related symptom improvement rate data are summarized in **Table 9**.

The symptom improvement rates were similar for the 2 dose groups. Of the 84 patients who had symptom improvement, the maximum LCS scores improved by a median of 7.0 points. Symptom improvement occurred soon after the start of treatment Median time (days) to improvement was 10.0 days and 9.0 days for the two treatment groups

Table 9: Rate of disease-related symptom improvements in Trial 39

Parameter	ZD1839 dose assignment	
	250 mg N=102	500 mg N=114
Number of patients with symptom improvement	44	40
Rate of response (%)	43.1	35.1
Lower 95% confidence interval	33.4	26.4
Upper 95% confidence interval	53.3	44.6

The median duration of symptom improvement was not calculable for the 250-mg/day group because 80% (35/44) of patients who had an improvement were still showing an improvement at the data cutoff. The median duration of symptom improvement was estimated at 164 days for the 500-mg/day group.

6.3.3.3 Progression-free survival

Progression-free survival was defined as the time from randomization to the assessment PD, death, or censoring at last assessment visit. The median progression-free survival was similar between the 2 dose groups: 59 days (95% CI: 56, 86) for the 250-mg/day group and 60 days (95% CI: 49, 67) for the 500-mg/day group.

6.3.3.4 Overall survival

As of the data cutoff of 1 August 2001, 53 (52.0%) of the patients in the 250-mg/day group were alive compared to 57 (50.0%) of the patients in 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.

6.3.3.5 QOL [FACT-L and TOI]

The FACT-L questionnaire contains a total of 34 questions, divided into 5 different domains: disease-related symptoms, physical, functional, emotional, and social. Each question is scored from 0 to 4. The Treatment Outcome Index (TOI) is the total score of disease-related symptom, physical, and functional questions. TOI changes of 6 points or more were found to be meaningful. The complete FACT-L questionnaire was filled out by patients every 28 days at the end of a treatment period. while disease-related symptom scores were obtained on a weekly basis

The highest QOL score (ie, the best QOL score) that can be attained for:

- FACT-L is 136
- TOI is 84

There were no significant differences (ie, 6 points for either FACT-L or TOI) in median baseline scores between the different groups for FACT-L and TOL Baseline scores for FACT-L ranged from 29.0 to 126.0, and for TOI ranged from 14.0 to 78.0. The overall compliance of filling out the questionnaire was 86%.

Summary of QOL findings

FACT-L improvement rate was higher in the 250-mg/day group (34.3%; 95% CI: 25.2%, 44.4%) than in the 500-mg/day group (22.8%; 95% CI: 15.5%, 31.6%).

TOI improvement rate was higher in the 250-mg/day group (33.3%; 95% CI: 24.3%, 43.4%) than in the 500-mg/day group (20.2%; 95% CI: 13.2%, 28.7%) (Summary Tables T4.4.2.1 and T4.4.2.2, Trial 39 CTR).

Time to FACT-L and TOI improvement was similar for each dose group with a median of 30 days (both FACT-L and TOI) for the 250-mg/day group and 29 days (TOI, 500-mg/day group) and 31 days (FACT-L, 500-mg/day group)

Because of the short time to data cutoff, many patients were censored, and there were not enough events to produce duration of improvement medians or confidence intervals for either FACT-L or TOL

The sponsor stated that all but 1 patient (95.5%, 21/22) of patients who showed a tumor response also showed an improvement in disease-related symptoms as measured by the LCS. The majority (77.4%, 65/84) of patients with disease control (PR+PRNM+SD) showed improvement in their LCS score with the stable disease patients having a 71.0% (44/62) symptom improvement rate. Patients with the best response of disease progression showed the smallest proportion (16.8%, 19/113) of patients with improved LCS scores. The FDA does not agree (see Executive Summary and page 64.

6.3.3.6 Disease Control – Sponsor Analysis

Patients defined as having disease control were those who had a best response rating of CR, PR (including PRNM) or SD that was maintained for at least 28 days from the first demonstration of that rating (ie, could not occur prior to 56 days from start of treatment).

The disease control rates were similar between the 2 dose groups: 42.2% (95% CI: 32.4%, 52.3%) in the 250-mg/day group and 36.0% (95% CI: 27.2%, 45.5%) in the 500-mg/day group. The median durations of disease control were similar in both dosage groups (125 days, 250-mg/day group; 111 days, 500-mg/day group). The duration of disease control was computed from the first post-baseline visit rather than the baseline visit. Time from randomization to disease progression would be approximately 28 days longer.

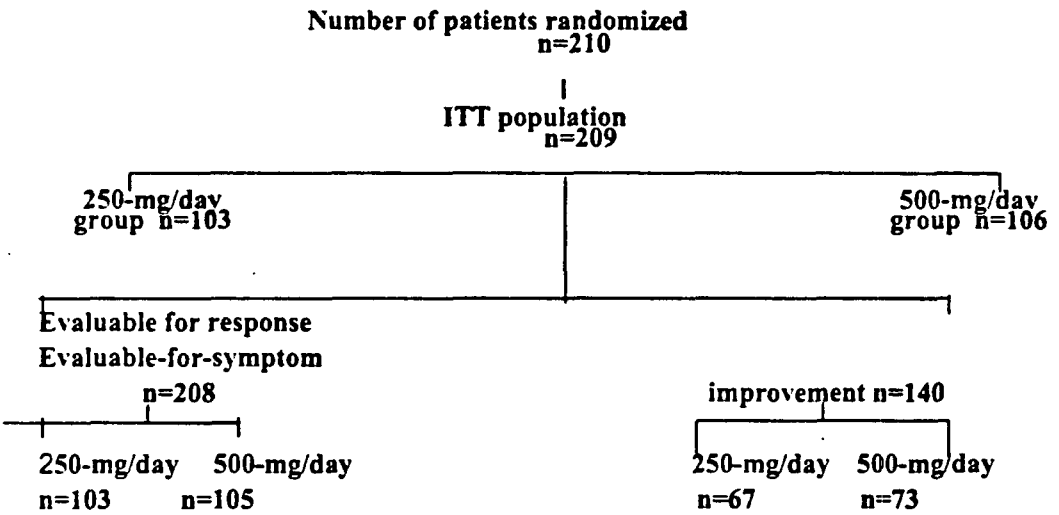
6.3.4 Supportive Trial 16 – Sponsor Analysis

6.3.4.1 Patient Population/Demography

Overall, 210 patients from 43 centers in Europe, Japan, and other countries around the world were randomized, of whom 209 received trial treatment. One patient was randomized but did not receive ZD1839 treatment due to a screening failure.

Patient populations are summarized graphically in **Figure 4**. Of the 209 patients treated (ITT population), 208 were considered evaluable for response and 140 were considered evaluable for symptom improvement.

Figure 4: Trial 16 patient populations



The demographic characteristics of these patients are summarized in **Table 10**.

Table 10: Demographic characteristics of patients in Trial 16

Demographic characteristic	Randomized treatment		
	ZD1839 250 mg/day (n= 104)	ZD1839 500 mg/day (n= 106)	All patients (n~2 10)
Age (years)			
Mean (standard deviation)	60.3(9.5)	58.9(9.7)	59.6(9.6)
Median	61.0	60.0	60.0
Range	28 to 85	37 to 78	28 to 85
Age group (number [%] of patients)			
18 to 64	69(66.3)	77(72.6)	146(69.5)
≥65	35(33.7)	29(27.4)	64(30.5)
Sex (number [%] of patients)			
Women	26(25.0)	36(34.0)	62(29.5)
Men	78(75.0)	70(66.0)	148(70.5)
Origin (number [%] of patients)			
White	49(47.1)	53(50.0)	102(48.6)
Black	2(1.9)	0	2(1.0)
Hispanic	2(1.9)	0	2(1.0)
Oriental	0	1 (0.9)	1 (0.5)
Japanese	51(49.0)	51(48.1)	102(48.6)
Other	0	1 (0.9)	1 (0.5)

Disease status/previous treatment at entry

The disease characteristics of patients at trial entry are presented in **Table 11.**

Table 11: Disease characteristics at trial entry in Trial 16

Characteristic	Randomized treatment ZD1839 250 mg/day (n= 104)	ZD1839 500 mg/day (n= 106)	All patients (n=210)
Previous cancer treatment, n			
Failed 1 previous chemotherapy regimen	104(100.0)	106(100.0)	210(100.0)
Failed 2 previous chemotherapy regimens	46 (44.2)	46 (43.4)	92 (43.8)
Prior Radiotherapy	52 (50.0)	48 (45.3)	100(47.6)
Prior Surgery	32 (30.8)	25 (23.6)	57 (27.1)
Other	4 (3.8)	9 (8.5)	13 (6.2)
WHO performance status (score), n (%)			
Normal activity (0)	18 (17.3)	20 (18.9)	38 (18.1)
Restricted activity (1)	73 (70.2)	72 (67.9)	145 (69.0)
In bed:<=50% of the time (2)	13 (12.5)	14 (13.2)	27 (12.9)
Histology type, n (%)			
Adenocarcinoma	64 (61.5)	68 (64.2)	132 (62.9)
Squamous	25 (24.0)	18 (17.0)	43 (20.5)
Large cell	9 (8.7)	9 (8.5)	18 (8.6)
Undifferentiated	3 (2.9)	8 (7.5)	11 (5.2)
Squamous and adenocarcinoma	3 (2.9)	3 (2.8)	6 (2.9)
Interval from diagnosis (months)			
Median/mean (months)	12.2/17.2	11.7/14.6	12.1/15.9
Minimum (months)	0.1	2.3	0.1
Maximum (months)	125	59.5	125
Current disease status, n (%)			
Locally advanced	25 (24.0)	20 (18.9)	45 (21.4)
Metastatic	79 (76.0)	86 (81.1)	165 (78.6)
Other tumor sites recorded at trial entry, n			
Adrenal	10 (9.6)	9 (8.5)	19 (9.0)
Liver	11 (10.6)	22 (20.8)	33 (15.7)
Bone	25 (24.0)	28 (26.4)	53 (25.2)
Lymph nodes	45 (43.3)	51 (48.1)	96 (45.7)
Lung	63 (60.6)	59 (55.7)	122 (58.1)
Skin/soft tissue	7 (6.7)	7 (6.6)	14 (6.7)
Brain	13 (12.5)	14 (13.2)	27 (12.9)
Other a	42 (40.4)	40 (37.7)	82 (39.0)

a Includes sites of pleural and pericardial effusion.

6.3.4.2 Treatment Response – Sponsor Analysis

Summary data for best overall objective response are presented in **Table 12**. A total of 119 (18.4%; 95% CI: 11.5%, 27.3%) patients showed partial responses in the 250-mg/day group. Twenty (19.0%; 95% CI: 12.1%, 27.9%) patients showed tumor

responses in the 500-mg/day group: 1 patient had a complete tumor response, 19 patients had partial responses. Patients with stable disease were distributed proportionately between groups with 37 (35.9% of the treatment group) in the 250-mg/day group and 34 (32.4% of the treatment group) in the 500-mg/day group.

Table 12: Investigator's assessment of best overall objective response:

Best tumor response	250 mg ZD1839 N=103	500 mg ZD1839 N=105
Complete response [n,	0	1(1.0)
Partial response + partial response in non-measurable disease [n,	18+1(18.4)	19+0(18.1)
Stable disease [n, (%)]	37(35.9)	34(32.4)
Progressive disease [n,	42(40.8)	44(41.9)

Overall, 17.9% of second-line patients had objective response, and 19.8% of third-line patients had objective response. There was no marked difference in response rates between patients who had failed 1 or 2 previous regimens regardless of whether they had prior docetaxel therapy. Responses occurred in patients with performance status of 2 (3.7%, 1/27) and in patients with non-measurable, evaluable disease (33.3%, 1/3). Women (34.4%, 21/61) appeared to have higher response rates than men (12.2%, 18/147). Responses occurred in almost all histologies, but occurred more often in adenocarcinomas (26.0%, 34/131) than in squamous (7.0%, 3/43) or other (6.3%, 2/32) histologies. Response rates were comparable in patients age 18-64 and those >=age 65 (19.4% and 17.2%, respectively. Responses were higher in a predominantly Japanese population than in the white population 25.9 and 11%, respectively.

The median duration of tumor response, as of 7/23/02, is 7.0 months (95% CI 5.7-8.9 mo, range 3.4-18.6+ mo.) for ZD1839 250 mg. And 5.8 (95% CI 4.5-11.7, range 4.4-15.6+) months for ZD1819 500 mg/day.

6.3.4.3 Disease-related symptom improvement –Sponsor Analysis

For Trial 16, patients were not required to be symptomatic for trial entry based on their baseline LCS scores. In order to evaluate disease-related symptom improvement in a symptomatic patient population (similar to Trial 39), a subset of the per-protocol population with a baseline

LCS score of <=24 was analyzed. Sixty-seven patients in the 250-mg/day group and 73 patients in the 500-mg/day group comprised the evaluable for symptom improvement population.

The overall compliance for the disease-related symptom questionnaire (LCS) was 74% and there was no apparent difference in compliance across the doses. Higher compliance was associated with a PS of 0 or 1 (vs PS 2), second-line (vs third-line), and Japanese (vs non-Japanese) patients.

LCS baseline characteristics

The distribution of each LCS item by score for all patients is presented in **Table 13.** Median baseline scores for LCS were 18.0 for the 2 dose groups indicating that this was a symptomatic population.

Table 13: Disease-related symptom distribution at baseline

Baseline score [n(%)]						
Disease-related symptom	N	Most Symptomatic		Less Symptomatic		No Symptoms
		0	1	2	3	4
Shortness of breath	140	16 (11.4)	29(20.7)	35(25.0)	43(30.7)	17(12.1)
Coughing	140	16(11.4)	29(20.7)	35(25.0)	31 (22.1)	29(20.7)
Chest tightness	136	3 (2.2)	18(13.2)	27(19.9)	37(27.2)	51(37.5)
Ease of breathing	138	19 (13.8)	23 (16.7)	42(30.4)	42(30.4)	12(8.7)
Weight loss	139	10(7.2)	16(11.5)	17(12.2)	36(25.9)	60(43.2)
Clarity of thinking	137	10(7.3)	16(11.7)	16(11.7)	43(31.4)	52(38.0)
Poor appetite	135	17(12.6)	19(14.1)	33(24.4)	41 (30.4)	25 (18.5)

Symptom improvement rate

The disease-related symptom improvement rate data are summarized in **Table 14.** The symptom improvement rates were similar for the 2 dose groups. Of the 54 patients who had disease-related symptom improvement, the maximum LCS score improved by a median of 7.0 points.

Table 14: Rate of disease-related symptom improvements

ZD1839 dose assignment Parameter	250 mg/day N=67	500 mg/day N=73
Patients with symptom improvement (n)	27	27
Rate of response (%)	40.3	37.0
Lower 95% confidence interval	28.5	26.0
Upper 95% confidence interval	53.0	49.1

6.3.4.4 Progression-free survival and overall survival

Progression-free survival

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

Overall survival

With a minimum follow-up of 4 months, 68% of patients in the 250-mg/day group and 79% in the 500-mg/day group were alive at data cutoff.

6.3.4.5 Subgroup analyses-Sex, Age, and Ethnicity

More women experienced tumor responses at either the 250-mg/day and 500/mg day doses (36.0%; 95% CI: 18.0%, 57.5% and 33.3%; 95% CI: 18.6%, 51.0%, respectively) than men (12.8%; 95% CI: 6.3%, 22.3% and 11.6%; 95% CI: 5.1%, 21.6%, respectively). No trend was seen for tumor response rates in either dose group between patients 18 to 64 years old and 65 years of age or older.

In Trial 16, where approximately one-half of the patients were Japanese, higher tumor response rates were seen in non-white patients in both the 250-mg/day dose group and 500-mg/day group (25.5% and 26.4%, respectively) than for white patients (10.4% and 11.5%, respectively).

Efficacy between Japanese and non-Japanese patients was more fully evaluated in Trial 16 and significant differences were observed with respect to tumor response, disease control, progression-free survival, and overall survival. Multivariate analyses showed that a portion of the differences were confounded with imbalances in baseline factors. This suggested 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. The results regarding a potential ethnic difference were inconclusive due to the non-randomized comparison, and the limitations of the data.

Symptom improvement by the subgroups sex, age, and ethnicity

The symptom improvement rates were similar between male and female patients in both dose groups: in male patients, 40.8% (95% CI: 27.0%, 55.8%; 250-mg/day group) and 34.8% (95% CI: 21.4%, 50.3%; 500-mg/day group), and in female patients, 38.9% (95% CI: 17.3%, 64.3%; 250-mg/day group) and 40.7%% (95%CI: 22.4%, 61.2%, 500-mg/day group). Likewise, symptom improvement rates by age or ethnicity were similar between dose groups.

In contrast to the other efficacy parameters, there was no significant difference observed for the disease-related symptom improvement rate between the Japanese and non-Japanese patients.

6.3.5 Detailed Review of Trial 39 – FDA Analysis

6.3.5.1 Study patients

Pivotal trial 39 eligibility required that patients must have failed prior platinum and docetaxel, given concurrently or sequentially, due to either progression on therapy or within 90 days of completion of therapy or because of unacceptable toxicity.

This eligibility criterion was met for 139 of the 216 ITT patients (64%) in this trial. The 139 number was obtained by querying Dataset RS00075 (Previous Cancer Treatment). Variable WDREAS (Reason for withdrawal) was used to select patients with progression or unacceptable toxicity (1=progressive disease and 9=unacceptable toxicity). The results of this query are summarized in **Table 15.**

Table 15: Patients refractory or intolerant to docetaxel and/or platinum

		Platinum Refractory/intolerant	
Taxotere Refractory/ Intolerant		Yes	No
	Yes	139	58
	No	11	8

6.3.5.2 Study Patient Summary

As might be expected, in a study that is enrolling locally advanced or metastatic NSCLC patients who have failed platinum, docetaxel and other chemotherapy and who still have a performance status of 0 to 2, the patients in this study are not typical of a population of newly diagnosed NSCLC patients of similar stage and performance status. The latter population might be expected to have a median survival of 6 to 9 months if stage IV at diagnosis and 16 to 18 months if stage III at diagnosis. Patients enrolled in this study have survived for a considerably longer time (see **Table 16** for data on time from lung cancer diagnosis to study randomization as well as other pertinent patient information). Striking is the percent of study patients with

adenocarcinoma alone or mixed with squamous cell carcinoma (73.6%). This is expected as adenocarcinoma has the slowest tumor doubling time of all lung cancer histologies

Table 16: Patient characteristics

Characteristic, n (%) of patients	ZD1839 dose		Total
	250 mg/day n=102	500 mg/day n=114	n=216
WHO performance status			
0	18 (17.6)	15 (13.2)	33 (15.3)
1	64 (62.7)	75 (65.8)	139 (64.4)
2	19 (18.6)	23 (20.2)	42 (19.4)
3	0	1 (0.9)	1 (0.5)
Not recorded	1 (1.0)	0	1 (0.5)
Tumor histology type			
Squamous	14 (13.7)	18 (15.8)	32 (14.8)
Adenocarcinoma	70 (68.6)	73 (64.0)	143 (66.2)
Squamous + adenocarcinoma	7 (6.9)	9 (7.9)	16 (7.4)
Undifferentiated	9 (8.8)	8 (7.0)	17 (7.9)
Large cell	2 (2.0)	3 (2.6)	5 (2.3)
Not recorded	0	3 (2.6)	3 (1.4)
Current disease status			
Locally advanced	15 (14.7)	9 (7.9)	24 (11. 1)
Metastatic	87 (85.3)	105 (92.1)	192 (88.9)
Months from diagnosis to randomization			
Median	23.8	16.6	19.6
<12 n (%)	20 (19.6)	39 (34.2)	59 (27.3)
12-24	32 (31.3)	34 (29.8)	66 (30.6)
25-36	26 (25.5)	28 (24.6)	54 (25.0)
37-48	12 (11.8)	2 (1.8)	14 (6.5)
49-60	6 (5.9)	5 (4.4)	11 (5.1)
>60	6 (5.9)	6 (5.3)	12 (5.6)
Number of prior chemotherapy regimens, n (%)			
1	2(2.0)	0	2 (0.9)
2	41(40.2)	48(42.1)	89 (41.2)
3	31(30.4)	41(36.0)	72 (33.3)
4 or more	28(27.5)	25(21.9)	53 (24.5)

6.3.5.3 Response rate – FDA Analysis

FDA agrees with the sponsor that there were 22 patients who had a partial response, 12 in the ZD1839 250 mg/day group and 10 in the 500 mg/day group. In 18 patients response was demonstrable by tumor measurements while 4 patients (3 in the 250 mg

group, 1 in the 500 mg group) had a PR in non-measurable disease. The response rate for the ITT population was 10.2% (95% C.I. 6.5%, 15%) The sponsor also determined the percent of patients who maintained stable disease but this was not felt to be a meaningful parameter because study patients likely had slow growing cancers.

6.3.5.4 Responder Characteristics

Characteristics of the 22 responding patients are summarized in **Tables 17 and 18**. Because of small numbers and comparable efficacy results patients receiving ZD1839 250mg/day and 500 mg/day are considered as one group in **Table 19**. While stage at diagnosis varied all patients had metastatic disease at the time of ZD1839 treatment.

Table 17: Responders – FDA Analysis

Center	Pt	Dose	Dx To Rand (m)	Age at Entry	Sex	PS	Histol	Stage at Dx	# Prior Regimens
2002	0287	250	10	53	F	2	Adeno	IV	3
2011	0166	500	50	73	F	2	Adeno	II	5
2011	0167	250	20	44	M	2	Adeno	IV	4
2011	0230	500	8	65	F	2	Squam	IIIB	2
2012	0293	500	16	42	F	1	Adeno	IIIA	3
2028	0111	500	34	68	F	1	Adeno	IV	5
2064	0077	250	28	67	F	1	Adeno	IV	4
2064	0084	250	13	41	F	1	Adeno	IV	3
2072	0141	500	21	68	F	2	Adeno	I	2
2090	0037	250	9	46	F	0	Adeno	IV	4
2090	0048	250	15	34	M	0	Undiff	IV	2
2090	0049	500	14	61	F	1	Adeno	IV	4
2090	0052	250	32	66	F	1	Squam	IV	4
2090	0217	250	33	51	F	0	Adeno	IIIB	4
2090	0222	500	17	70	M	1	Adeno	IIIA	2
2118	0170	250	14	61	F	1	Adeno	IV	2
2201	0258	500	17	47	F	1	Adeno	IIIB	3
2255	0302	250	18	60	F	1	Adeno	IIIB	3
2255	0338	250	21	80	F	2	Adeno	IIIA	3
2255	0340	500	19	70	M	0	Adeno	IV	3
2256	0250	250	52	46	F	1	Adeno	IV	2
2271	0197	500	28	58	F	1	Adeno	IV	2

Table 18: Responder characteristics - ITT Population

Characteristic	Number of responders
Sex	
Female	18/93
Male	4/123
Histology	
Adenocarcinoma	19/143
Squamous	2/32
Undifferentiated	1
Months from diagnosis to ZD1839 randomization	
<12	3
13-24	12
25-36	5
≥50	2
Prior chemotherapy regimens (n)	
2	7
3	7
4	6
5	2

Thirteen of the 22 responders were stage IV at diagnosis. The median number of months from diagnosis to study randomization for this group of patients was 19 months, range 9 to 52 months.

Table 19 summarizes the number of measurable lesions for 18 of the 22 responding metastatic disease NSCLC patients (4 patients had only evaluable disease). As indicated the majority of responding patients had only 1 or 2 lesions that were measured. The site of the measurable lesion in patients with only one measurable tumor was lung in 4 patients and liver in one patient. The site of the measurable lesion in patients with two measurable tumors was lung only in 2 patients, lung and liver in 2 patients, lung and lymph node in 1 patient and liver only in 1 patient. Baseline total tumor area of measurable lesions was less than 10 cm2 in 5 of 18 responding patients with measurable lesions

Table 19: Number of measurable lesions evaluated in responding patients - FDA

Measurable lesions (n)	Responding patients (n)
0	4
1	5
2	6
3	2
4	3
6	1
8	1

Among the 139 patients deemed by the FDA to be platinum/taxotere refractory/intolerant there were 14 patients with a partial response, (response rate 10.1%, (95% C.I. 5%, 17%). These patients are listed in **Table 20**.

Table 20: Responders refractory/intolerant to platinum and docetaxel - FDA

Center	Pt	Dose	Dx To Rand (m)	Age at Entry	Sex	PS	Histol	Stage at Dx	# Prior Regimens
2002	0287	250	10	53	F	2	Adeno	IV	3
2011	0167	250	20	44	M	2	Adeno	IV	4
2011	0230	500	8	65	F	2	Squa	IIIB	2
2028	0111	500	34	68	F	1	Adeno	IV	5
2064	0084	250	13	41	F	1	Adeno	IV	3
2072	0141	500	21	68	F	2	Adeno	I	2
2090	0037	250	9	46	F	0	Adeno	IV	4
2090	0048	250	15	34	M	0	Undiff	IV	2
2090	0049	500	14	61	F	1	Adeno	IV	4
2090	0052	250	32	66	F	1	Squa	IV	4
2090	0217	250	33	51	F	0	Adeno	IIIB	4
2118	0170	250	14	61	F	1	Adeno	IV	2
2255	0338	250	21	80	F	2	Adeno	IIIA	3
2255	0340	500	19	70	M	0	Adeno	IV	3

It is of interest that response rates of the 139 patient doubly refractory/intolerant population and the remaining 77 patient less refractory/intolerant population (8 responses) were comparable. Higher response rates are generally expected in less refractory patients.

6.3.5.5 Response and Performance Status – FDA Analysis

Because performance status is universally recognized as an important, and possibly the most important, prognostic factror for survival it was of interest to explore whether treatment response was associated with improvement of performance status. This

analysis should be considered as hypothesis generating as it had not been prespecified in the protocol and because benefit was arbitrarily determined to be an improvement of one PS grade on two consecutive observations. For the 22 responding patients;

5 patients were PS 0 at baseline and maintained that PS throughout treatment.

17 patients were PS 1 or 2 at baseline. Of those patients

9/17 improved their PS by 1 grade,

1/17 improved PS by 2 grades,

1/17 had a PS decline of 2 grades,

6/17 maintained their PS throughout treatment.

6.3.5.6 Performance Status and Quality of Life Relationships

It was also of interest to compare PS score (generated by a physician or other health care professional and quality of life score generated by the patient (**Table 21**). Two quality of life scales, the lung cancer subscale (LCS) and treatment outcome index (TOI) were compared. On the LCS patients would score 28 if they had no shortness of breath, no weight loss, clear thinking, no cough, good appetite, no chest tightness and easy breathing and would score zero if they were very affected by the above symptoms. The TOI is the sum of the LCS + the 7 item physical well being component (lack of energy, nausea, trouble meeting needs of family, pain, side effects of treatment, feeling ill and forced to spend time in bed) + the 7 item functional well being component (able to work [including work at home], work is fulfilling, enjoyment of life, accepting illness, sleeping well, enjoyment of things done for fun, contentment with quality of life). Total TOI score ranges from 0 = very adversely affected to 84 = not at all adversely affected. The scoring system for the LCS is that a change of $\geq +2$ will be considered improved, ≤ -2 worsened, otherwise no change. The scoring system for the TOI is that a change of $\geq +6$ was considered improved, ≤ -6 worsened, otherwise no change.

Table 21: Comparison of baseline PS and baseline LCS and TOI – FDA

		Lung Cancer Subscale		Treatment Outcome Index	
PS	Patients (n)	Median	Range	Median	Range
0	33	19	11-24	55	20-75
1	139	17	2-27	49	14-78
2	42	15	8-23	43	23-66

PS is universally recognized as the most important prognostic factor for efficacy and toxicity in advanced/metastatic disease non-small cell lung cancer. The observation that there was wide variation in LCS and TOI scores for each PS score suggests a complex interrelationship between these variables. Perhaps patients with PS 0 and a high LCS and /or TOI score will do especially well.

6.3.5.7 Progression free survival

FDA analysis agrees with sponsor analysis. Median time from randomization to progression or death was 59.0 days (95% CI 56.0-86.0) for the 102 patients treated with ZD1839 250 mg/day and 60.0 days (95% CI 49.0-67.0) for the 114 patients treated with ZD1839 500 mg/day.

6.3.6 Detailed Review of Trial 16 per FDA

Two-hundred ten patients from 43 centers in Europe, Japan and other countries around the world were randomized. One randomized patient was not treated leaving 209 patients in the ITT population.

6.3.6.1 Patient Demographics and Disease Characteristics

Pertinent demographic characteristics are summarized in **Table 22.**

Table 22: Trial 16 Demographic characteristics

Characteristic	Randomized treatment		
	ZD1839 250 mg/day (n= 104)	ZD1839 500 mg/day (n= 106)	All patients (n=210)
Age (years)			
Median	61.0	60.0	60.0
Range	28 to 85	37 to 78	28 to 85
Sex (number [%] of patients)			
Women	26 (25.0)	36 (34.0)	62 (29.5)
Men	78 (75.0)	70 (66.0)	148 (70.5)
Origin (number [%] of patients)			
White	49 (47.1)	53 (50.0)	102 (48.6)
Black	2 (1.9)	0	2 (1.0)
Hispanic	2 (1.9)	0	2 (1.0)
Oriental	0	1 (0.9)	1 (0.5)
Japanese	51 (49.0)	51 (48.1)	102 (48.6)
Other	0	1 (0.9)	1 (0.5)

Disease characteristics of study 16 patients are listed in **Table 23.**

Table 23: Disease characteristics at trial entry in Trial 16

Characteristic	Randomized treatment ZD1839 250 mg/day (n= 103)	ZD1839 500 mg/day (n= 106)	All patients (n=209)
Previous cancer chemotherapy, n (%)			
Platinum as first or second line Rx	103(100.0)	106(100.0)	209(100.0)
Progression on first line therapy	26 (25.2)	29 (27.4)	55 (26.3)
Progression on second line therapy	23 (22.3)	12 (11.3)	35 (16.7)
Progression on either 1st or 2nd line chemo	36 (35.0)	37 (34.9)	73 (34.9)
No progression on chemotherapy	67 (65.0)	69 (65.1)	136 (65.1)
WHO performance status (score), n (%)			
0	18 (17.3)	20 (18.9)	38 (18.1)
1	73 (70.2)	72 (67.9)	145 (69.0)
2	13 (12.5)	14 (13.2)	27 (12.9)
Histology type, n (%)			
Adenocarcinoma	64 (61.5)	68 (64.2)	132 (62.9)
Squamous	25 (24.0)	18 (17.0)	43 (20.5)
Large cell	9 (8.7)	9 (8.5)	18 (8.6)
Undifferentiated	3 (2.9)	8 (7.5)	11 (5.2)
Squamous and adenocarcinoma	3 (2.9)	3 (2.8)	6 (2.9)
Interval from diagnosis (months)			
Median/mean (months)	12.2/17.2	11.7/14.6	12.1/15.9
Minimum (months)	0.1	2.3	0.1
Maximum (months)	125	59.5	125
Current disease status, n (%)			
Locally advanced	25 (24.0)	20 (18.9)	45 (21.4)
Metastatic	79 (76.0)	86 (81.1)	165 (78.6)

6.3.6.2 Objective Response Rate

Table 24: Objective response rate ITT population:

Best tumor response	250 mg ZD1839 N=103	500 mg ZD1839 N=106	Total N= 209
Complete response [n, (%)]	0	1 (1.0)	1 (0.5)
Partial response [n, (%)]	19 (18.4)	19 (18.2)	38 (18.2)

6.3.6.3 Responder Characteristics

Tables 25 and 26 summarizes disease status of the 39 responding patients.