

Briefing Document

NDA 21-399

Drug Name

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Documents reviewed

EDR Submissions

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Executive Summary

ZD 1839 (Iressa™) is a new class of drug that inhibits Epidermal Growth Factor Receptor (EGFR) tyrosine kinase activity. 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.

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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.

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

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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

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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.

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

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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

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relief analysis. There are also methodologic issues including early progressors being censored, and the use of concomitant medications that might have contributed to symptom relief.

Overall Conclusions-FDA: While there are hints of drug activity, i.e. an objective response rate of 10.8% in the third-line treatment setting, the absence of a non- ZD1839 treated control group makes it difficult to evaluate these 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 as all patients received ZD1839, dropout of patients with early disease progression and meaningfulness of the criteria used to designate benefit.

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.

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.

These results raise a question regarding accelerated approval of Iressa. Accelerated approval regulations require additional studies that demonstrate clinical benefit. Can FDA consider accelerated approval when it has already been demonstrated in the INTACT trials that there is no survival advantage?

Clinical Review

1. Introduction and Background

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

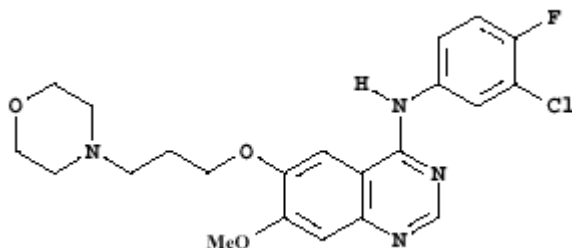
1.1.1 Proposed Indication

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 C₂₂H₂₄ClFN₄O₃ and molecular weight of 446.9.

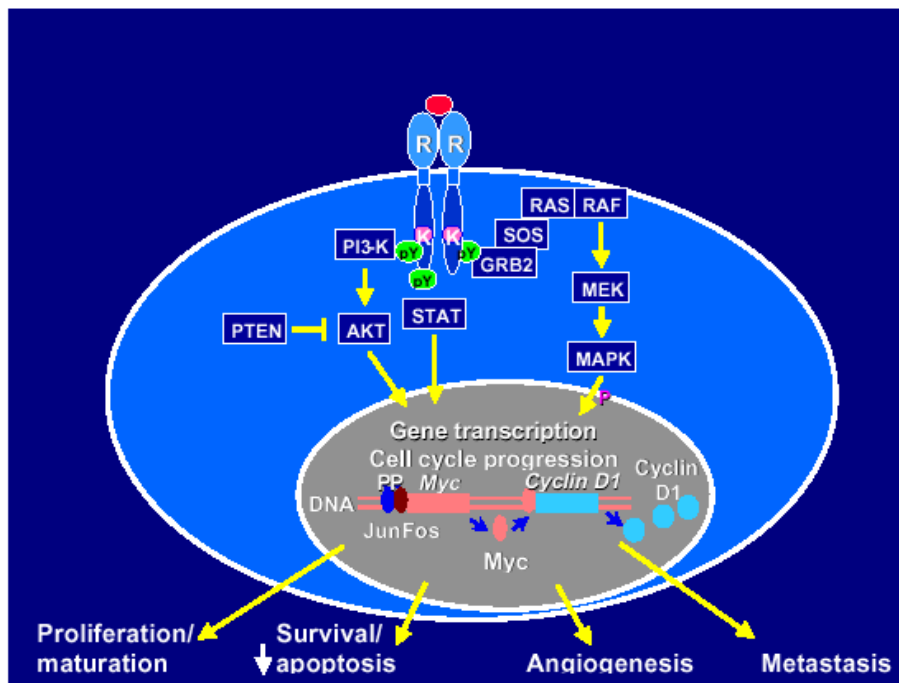
Figure 1: Molecular Structure of ZD1839



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:

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- 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 clarified
- 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

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- 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 performance 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 A431 tumor 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 TGF α . 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 [^{14}C]-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 1 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 ZD1839 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 1 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 ZD1839 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.

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- In cancer patients within a dose group, measures of steady state exposure (C_{min}) to ZD1839 between individuals span up to a 16-fold range of values.
- Within an individual, measures of steady state exposure (C_{min}) 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.

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 protocol, 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

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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

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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 checklist ^f					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.

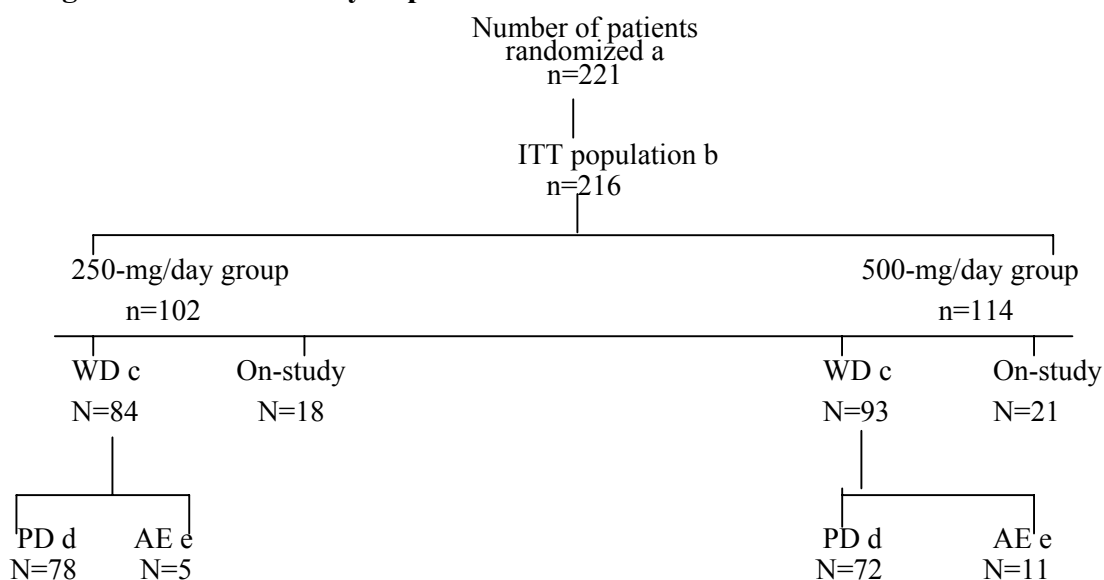
b Tumor assessment was required within 14 days before randomization, approximately 28 days and 56 days after randomization, and approximately every 8 weeks thereafter.

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.

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Table 3: Demographic characteristics, ITT population in Trial 39

Characteristic	250 mg/day N=102	ZD1839 dose 500 mg/day N= 114	Total 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).

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

Characteristic, n (%) of patients	ZD1839 dose		Total N=216
	250 mg/day N=102	500 mg/day N=114	
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.

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

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

Characteristic	ZD1839 dose		Total N=216
	250 mg/day N=102	500 mg/day N=114	
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**.

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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.

The majority of tumor responses (77.3%, 17/22) were ongoing at the time of data cutoff (minimum follow-up of 4 months). The median duration of tumor response could not be calculated for the 250-mg/day group (10 of the 12 patients have not progressed); the median duration of tumor response for the 500-mg/day group was estimated at 136 days.

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The range of duration of tumor responses was 1+ to 7+ months in the 250-mg/day group and 2+ to 4+ months in the 500-mg/day group.

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				No
		<u>Symptomatic</u>		<u>Symptomatic</u>		<u>Sx</u>
		0	1	2	3	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.

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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	<u>ZD1839 dose assignment</u>	
	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

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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.

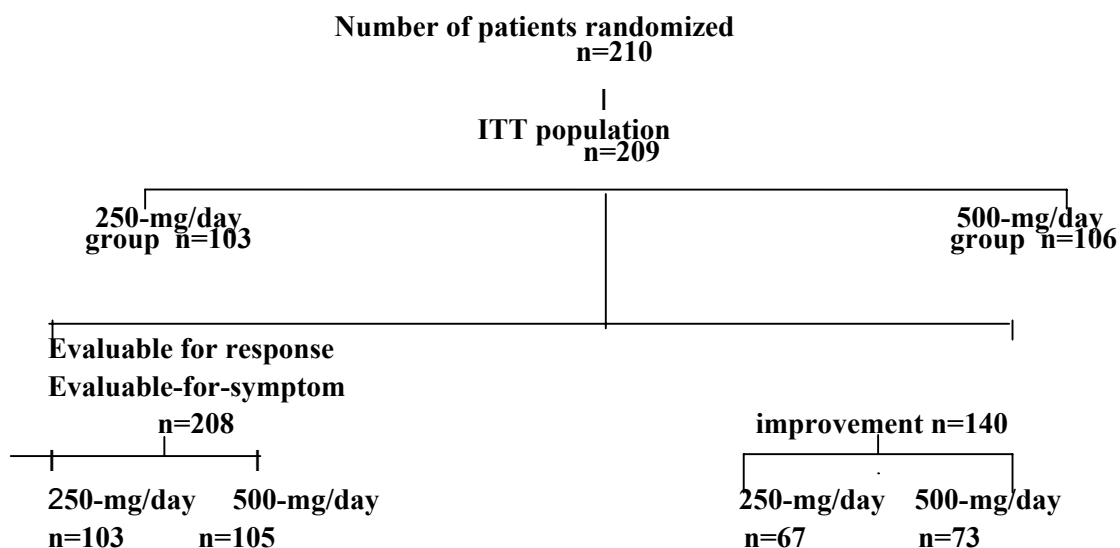
6.3.4 Supportive Trial 16 – Sponsor Analysis

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**.

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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**.

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Table 11: Disease characteristics at trial entry in Trial 16

Characteristic	Randomized treatment		All patients (n=210)
	ZD1839 250 mg/day (n= 104)	ZD1839 500 mg/day (n= 106)	
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

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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 \geq 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 could not be calculated for either dosage group. The majority of tumor responses (87.2%, 34/39) were ongoing at the time of data cutoff.

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

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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	500 mg/day
	N=67	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

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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 n=216
	250 mg/day n=102	500 mg/day n=114	
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

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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

Cen ter	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

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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

Cen ter	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		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		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

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Because performance status is universally recognized as an important, and possibly the most important, prognostic factor 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

PS	Patients (n)	Lung Cancer Subscale		Treatment Outcome Index	
		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

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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**.

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Table 23: Disease characteristics at trial entry in Trial 16

Characteristic	Randomized treatment		All patients (n=209)
	ZD1839 250 mg/day (n= 103)	ZD1839 500 mg/day (n= 106)	
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 1 st or 2 nd 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.

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Table 25: Responder characteristics – Trial 16

CEN TER	PT	DOSE	HISTOL	STAGE			PS	SEX	ORIGIN	AGE	MOs
				T	N	M					DIAG
0712	0002	500	Adeno	3	0	1	1	F	Cauc	60	7.8
0259	0001	250	Adeno	3	2	0	1	F	Cauc	59	15.6
0415	0004	250	Squam	4	2	0	0	M	Cauc	61	21.7
0415	0006	500	Ad&Sq	4	3	1	1	M	Cauc	70	17.3
0416	0006	500	Adeno	4	0	1	1	F	Cauc	68	15.3
0601	0001	500	Adeno	4	0	1	1	M	Cauc	59	12.7
0601	0002	500	Adeno	4	0	1	1	F	Cauc	54	18.6
0601	0004	250	Adeno	4	0	1	1	F	Cauc	52	8.3
0601	0007	250	Adeno	0	3	1	0	M	Cauc	59	4.1
0916	0006	500	Undiff	4	2	1	1	M	Cauc	69	15.4
0111	0001	250	Adeno	0	3	1	0	F	Cauc	74	84.6
0804	0003	250	Adeno	2	0	1	0	F	Japan	59	10.1
0804	0001	500	Adeno	4	0	1	1	F	Japan	59	14.4
0803	0003	500	Adeno	3	2	1	0	M	Japan	71	11.3
0802	0001	250	Adeno	3	2	1	1	M	Japan	67	1.8
0801	0004	250	Squam	4	0	1	1	F	Japan	74	6.2
0801	0003	250	Adeno	4	0	1	1	F	Japan	61	15.4
0800	0001	500	Adeno	4	2	1	1	F	Japan	57	26.9
0805	0011	250	Adeno	0	0	1	1	M	Japan	59	ND
0800	0003	250	Adeno	0	0	1	1	M	Japan	56	28.1
0815	0007	250	Adeno	2	0	1	1	F	Japan	70	12.2
0822	0004	250	Adeno	4	2	0	1	M	Japan	53	13.8
0821	0003	500	Adeno	4	2	1	1	F	Japan	51	18.1
0821	0002	500	Adeno	4	3	1	1	M	Japan	37	7.6
0819	0009	250	Adeno	2	0	1	1	M	Japan	61	1.9
0819	0008	500	Adeno	4	0	0	0	M	Japan	52	15.9
0819	0007	500	Adeno	4	3	1	1	M	Japan	58	7.5
0819	0006	500	Adeno	4	2	0	1	M	Japan	40	3.7
0804	0005	250	Adeno	4	1	1	1	F	Japan	54	9.3
0818	0002	500	Adeno	4	2	1	1	F	Japan	55	17.4
0805	0009	250	Adeno	4	3	1	1	F	Japan	67	16.8
0815	0005	250	Adeno	0	2	1	1	M	Japan	28	ND
0815	0002	250	Adeno	0	0	1	1	M	Japan	60	54.0
0814	0012	250	Adeno	2	2	1	2	M	Japan	69	16.4
0814	0003	500	Adeno	4	3	1	1	F	Japan	61	11.0
0813	0002	500	Adeno	4	2	1	1	F	Japan	57	21.8
0807	0004	500	Squam	2	2	1	0	F	Japan	63	8.2
0807	0001	500	Adeno	4	0	0	1	F	Japan	64	ND
0818	0003	500	Adeno	4	3	1	1	F	Japan	74	23.0

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ND = no data

Table 26: Summary of Responder Characteristics

Characteristic	n (%)
Age	
Median	59
Range	28 - 74
Sex	
Male	18 (46.2)
Female	21 (53.8)
Origin	
Caucasian	11 (28.2)
Japanese	28 (71.8)
ZD1839 Dose	
250 mg	19 (48.7)
500 mg	20 (51.3)
Histology	
Adenocarcinoma	34 (87.2)
Adenocarcinoma+squamous cell	1 (2.5)
Squamous cell	3 (7.7)
Undifferentiated	1 (2.5)
Performance Status	
0	7 (17.9)
1	31 (79.5)
2	1 (2.6)
Stage	
M0	5 (12.8)
M1	34 (87.2)
Months from diagnosis	
Median	14.9
Range	1.8 - 84.6

6.3.6.3 Chemotherapy Sensitivity/Resistance of Responding Patients

Responder resistance/sensitivity to prior chemotherapy is summarized in **Table 27**. Twenty-nine of the 39 responders had not progressed on any prior chemotherapy treatment.

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Table 27: All Responders - Prior chemotherapy and outcome

Prior chemotherapy	N (%)
Number of Prior chemotherapy regimens	
1	21 (53.8)
2	18 (46.2)
Progression on first-line chemotherapy	6 (15.4)
Progression on second-line chemotherapy only	3 (7.7)
Progression on both 1 st & 2 nd line chemotherapy	1 (2.5)
No progression on chemotherapy	29 (74.4)

Two episodes of progression were not included in this table. One patient 804/03 was recorded as having progressed on second line treatment on the day of treatment and a second patient 819/06 was deemed to have progressive disease one day after first-line treatment. Among the responding patients that had progressed on prior chemotherapy there were 2 Caucasians and 8 Japanese, including the one patient 805/11 who progressed on both first- and second-line treatment..

Table 28 summarizes the number of measurable lesions for 38 of 39 patients with measurable lesions who had an objective tumor response. As indicated the majority of responding metastatic disease patients had only one or two lesions that were measured. Baseline total area of measurable lesions was less than 10 cm² in 3 of 11 Caucasian patients and 11 of 21 Japanese patients who had measurable lesions and who responded to therapy. Baseline total area of measurable disease was <5 cm² in 6 Japanese patients and no Caucasian patients

Table 28: Number of measurable lesions evaluated in responding patients

Measurable lesions (n)	Responding patients (n)
0	1
1	16
2	12
3	5
4	3
6	1
8	1

Table 29 demonstrates site(s) of measurable and non-measurable disease for the 39 responding patients. Nineteen responders had lung only disease (primary tumor site

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with or without contralateral lung involvement. The second most common sites of involvement were lung plus regional lymph node disease (6 patients).

Table 29: Sites of Measurable/Evaluable Disease

Measurable and non-measurable tumor location	Responding patients (n=39)
Lung only	19
Lung + nodes	6
Lung + nodes + adrenal	1
Lung + nodes + liver	1
Lung + nodes + bone	2
Lung + bone	4
Lung + bone + liver	1
Lung + liver	1
Lung + subcutaneous	1
Nodes only	2
Nodes + adrenal + liver	1

6.3.7 Reviewer Efficacy Conclusions Trials 39 and 16

There are several bothersome issues raised by the Iressa efficacy review. These are listed below.

1. Study eligibility –

Accelerated approval requires an improvement over available therapy. In advanced/metastatic NSCLC the clinical setting where there is no “available therapy” is third-line chemotherapy. Therefore, Trial 39 eligible patients must have received at least two prior chemotherapy regimens including 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.

Trial 16 did not address an unmet medical need and it is, therefore, only a supporting study. In Trial 16 eligible 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, both presumably indicating the presence of chemotherapy resistant disease. In fact, however, only 35% of study patients were

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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 (see paragraph 4).

2. Study patient characteristics

As might be expected from the treatment eligibility requirements of trial 39, the enrolled study population, i.e. (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. It is uncertain as to whether patient symptomatology was primarily due to tumor or to comorbid illness.

Trial 16 patients, like trial 39 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%).

3. Treatment response

Based on response criteria, a patient who had measurable disease, with or without non-measurable but evaluable disease or non-measurable/non-evaluable disease, could not be declared a responder unless there was $\geq 50\%$ decrease in the sum of the area of measurable lesions. 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. Similarly, in Trial 16, among the 38 responding patients with measurable lesions, 16 patients had only a single lesion measured and 12 had two lesions measured. As smaller lesions are more likely to respond to chemotherapy than larger lesions, if for no other reason than measurement error, 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 16 baseline total area of measurable lesions was less than 10 cm² in 3 of 11 Caucasian patients and 11 of 21 Japanese patients who had measurable lesions and who responded to therapy. Baseline total area of measurable disease was <5 cm² in 6 Japanese patients and no Caucasian patients. 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 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).

4. 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 one accepts this premise then it is to be expected 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 patients who have failed less than two regimens. This was not the case. Response rates of both groups were approximately 10%. The constancy of response rates in patients progressing on two or more chemotherapy regimens, patients progressing on one regimen and patients not refractory to any chemotherapy is of concern.

6 Integrated Review of Safety

7.1 Brief Statement of Conclusions

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. Dose reductions due to toxicity occurred in 1.0% of patients at the 250-mg dose versus 8.8% 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. There was no evidence of cumulative toxicity, and the majority of drug-related adverse events were reversible.

In study 16, similar to study 39, 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. Drug-related adverse events experienced by at least 10% of patients in the 250-mg/day group were rash, diarrhea, pruritus, dry skin, nausea, acne, SGPT/ALT increased, and

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SGOT/AST increased. There was no evidence of cumulative toxicity, and the majority of drug-related adverse events were reversible.

7.2 Patient Exposure

In the Phase II trials, 425 patients were exposed to ZD1839 (216 patients in Trial 0039, and 209 patients in Trial 0016). The majority of patients in both trials received ZD1839 for >1 month, with approximately one-third receiving ZD1839 for >3 months. Duration of exposure in Trials 0039 and 0016 is summarized in **Table 30**. Thirty-one patients (15.1%) who received ZD1839 250 mg daily had an interruption in therapy, and 1 patient (0.5%) had a dose reduction due to toxicity. This compares to 56 (25.5%) and 21 (9.5%) patients, respectively, who received ZD1839 500 mg daily (**Table 31**).

In the Phase I multiple-dose trials, 270 patients were exposed to a range of doses of ZD1839 from 50 to 1000 mg daily. Nearly half the patients (46.7%) received ZD1839 for >1 month, with 47 patients (17.4%) receiving ZD1839 for >3 months. Nineteen (7.0%) patients had dose reductions due to toxicity; all occurred at doses ≥ 300 mg/day, with 14 occurring in the 72 patients who received doses ≥ 600 mg/day.

Table 30: Duration on trial and duration of treatment

Category	Trial 0039		Trial 0016	
	250 mg (n=102)	500 mg (n=114)	250 mg (n=103)	500 mg (n=106)
Number of days on trial ^a				
Mean (standard deviation)	75.7(53.0)	69.5(49.9)	87.0(53.9)	86.9(57.9)
Maximum	232	232	229	219
Number of days on treatment ^b				
Mean (standard deviation)	72.6(51.9)	62.7(47.3)	85.1 (54.2)	81.5(56.5)
Maximum	213	232	227	219
Number of months on treatment (number [%] of patients)				
<1 month	41 (40.2)	38(33.3)	19(18.4)	27(25.5)
1 to 3 months	24(23.5)	41 (36.0)	46(44.7)	39(36.8)
>3 to 6 months	36(35.3)	34(29.8)	34(33.0)	33 (31.1)
>6 to 8 months	1 (1.0)	1(0.9)	4(3.9)	7(6.6)

^a a date of last dose minus date of first dose plus 1, ignoring any dose interruptions.

^b days of drug exposure: time from first dose to last dose minus the number of days off treatment. If a patient withdrew at the end of a treatment interruption his/her exposure would be underestimated by the length of the final interruption.

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FDA comment: Duration of treatment confirmed using dataset THR1639.

Table 31: Patients with therapy interruptions or dose reductions due to toxicity

Category	Number (%) of patients			
	Pivotal Trial 0039		Supportive Trial 0016	
	250 mg (n= 102)	500 mg (n= 114)	250 mg (n= 103)	500 mg (n=106)
Therapy interruption	15(14.7)	26(22.8)	16(15.5)	30(28.3)
Dose reduction	1 (1.0)	10(8.8)	0(0.0)	11(10.4)

In both trials, the proportion of patients who had interruptions in therapy was lower in the 250mg/day group than in the 500-mg/day group. These interruptions were spread throughout the treatment periods with the highest number occurring during the first 28 days. The main reasons for interrupting therapy were skin reactions and GI disturbances.

Across the 2 trials, there was only 1 (0.5%) dose reduction in the 250-mg/day group compared to 21 (9.5%) in the 500-mg/day group. The occurrence of these dose reductions in the patient population was distributed throughout the treatment periods and was frequently associated with skin reactions and GI disturbances.

FDA comment: Dose reductions and delays in drug treatment are confirmed using dataset THR1639.

Phase I trials: patients with solid tumors

The exposure of patients with solid tumors to ZD1839 in the Phase I multiple-dose trials is presented in **Table 32**.

Table 32: ZD1839 Exposure in Phase I multiple-dose trials

Exposure	Trial				
	0005 (n=64)	0011 (n=69)	0012 (n=88)	0038 (n=18)	V-15-11 (n=31)
Total days of dosing					
Total	2241	6808	6239	458 a	1048
Mean	35.0	98.7	70.9	25.4	33.8
Median	28b	56	43	28	14
Minimum	1	1	5	7	2
Maximum	205a	506	458	28	182c

a Only includes data collected for the first 28-day treatment period.

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b Because of the dosing schedule in Trial 0005 (ie, 14 days with drug, 14 days without), 28 days is equivalent to 2 months on trial, and 205 days is equivalent to 14 months on trial.

c Because of the dosing schedule in Trial V-15-11 (ie, 14 days with drug, 14 days without), 182 days is equivalent to 13 months on trial.

The exposure of patients to ZD1839 within these dose categories is presented in **Table 33**.

Table 33: Exposure to ZD1839 in the Phase I trials, by dose category

Exposure ZD1839 dose category	<225 mg (n=51)	250 mg a (n=75)	500 mg b (n=72)	>525 mg (n=72)
Total days of dosing				
Total	2356	5776	3883	4780
Mean	46.2	77.0	53.9	66.4
Minimum	1	1	7	5
Maximum	458	506	404	395
Number of months on Rx (number [%] of patients)				
<1 month	38(74.5)	31(41.3)	41(56.9)	34(47.2)
1 to 3 months	10(19.6)	28(37.3)	19(26.4)	22(30.6)
>3 to 6 months	1(2.0)	8(10.7)	9(12.5)	10(13.9)
>6 months	2(3.9)	8(10.7)	3(4.2)	6(8.3)

a Including doses between 225 mg and 300 mg, inclusive.

b Including doses between 400 mg and 525 mg, inclusive.

In Trial 0035, nineteen patients received a single 50 mg iv dose of ZDI 839, and 17 of these patients also received a single 250 mg oral dose of ZD1839.

Dose reductions

None of the 95 patients in Trials 0005 and V-15-11 (16 of whom received 525 mg/day ZD1839, and 15 of whom received 700 mg/day ZD1839) had a dose reduction.

In Trial 0011, a total of seven (10.1%) patients had a dose reduction attributed to drug-related adverse events; treatment in 6 of these patients was also interrupted because of toxicity. All reductions or interruptions of trial medication occurred in patients assigned to doses of ≥ 600 mg/day.

In Trial 0012, nine (10.2%) patients had a dose reduction attributed to drug-related adverse events; treatment in all of these patients was also interrupted because of toxicity. All reductions or interruptions of trial medication occurred in patients assigned to doses of at least 300 mg/day; 7 out of 9 dose reductions occurred among the 40 patients who were assigned ≥ 600 mg/day.

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In Trial 0038, three (16.7%) patients stopped taking the 500 mg daily dose of ZD1839 due to adverse events. Treatment was interrupted in each case, and all 3 patients subsequently resumed ZD1839 treatment at the lower dose of 250 mg daily.

FDA Comment: Data on drug exposure, dose reductions and dose delays was confirmed in Section 5 of the sponsor safety report of each individual study. Specific datasets containing this data were not provided.

7.3 Safety Review Methods and Findings

Sponsor safety data bases for **study 39** 9AE, AE FLGS, LAB, LAB 1096, LAB 1097, LABS, RS01409, RS01438, RS01438a, S00103, S01363, and for **study 16** ADVERSE, ECG, LAB01096, LAB01097, RS01438, S01949, S01963, S01964, S01965, S01966, SCHIRMER, SKINCHAR, TRANSAM.

FDA Comment: In the analysis of AE's the sponsor's convention of not counting an AE if it was present before the start of treatment (irrespective of how long it persisted after the start of treatment was followed. While this was an arbitrary decision any other method for counting AE's would be equally arbitrary.

7.3.1 Overview of adverse events

An overview of adverse events occurring in Trial 0039, by the dose of ZD1839 received at trial entry, is summarized in **Table 34**.

Table 34: Overview of adverse events in Trial 0039

Category	Number (%) of patients	
	250 mg/day (n=102)	500 mg/day (n=114)
All adverse events	101 (99.0)	112(98.2)
drug related	74(72.5)	97(85.1)
Deaths		
due to adverse event(s)	6(5.9)	5(4.4)
due to drug-related adverse event(s)	0(0.0)	1 (0.9)
Withdrawals		
due to adverse event(s)	4(3.9)	11 (9.6)
due to drug-related adverse event(s)	1(1.0)	5(4.4)
due to serious adverse event(s)	4(3.9)	8(7.0)
due to drug-related serious adverse event(s)	1(1.0)	1(0.9)
Serious adverse events	28(27.5)	27(23.7)
drug-related	4(3.9)	5(4.4)
CTC Grade 3 or 4 adverse events	41 (40.2)	53(46.5)
drug related	7(6.9)	20(17.5)

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The most frequent adverse events experienced by $\geq 25\%$ of patients receiving ZD1839 250 mg/day were diarrhea (56.9%), rash (48.0%), asthenia (28.4%), dyspnea (28.4%), nausea (26.5%), and acne (25.5%). Some adverse events, most notably diarrhea, rash, asthenia, acne, and dry skin, occurred less frequently in patients receiving ZD1839 250 mg/day than patients receiving 500 mg/day. Those adverse events with an incidence of $\geq 10\%$ in either dose group are presented in **Table 35**.

Table 35: Adverse events with an incidence of $\geq 10\%$ in Trial 39

Adverse event	Number of patients	
	250 mg/day (n=102)	500 mg/day (n=114)
Diarrhea	58 (56.9)	85 (74.6)
Rash	49 (48.0)	63 (55.3)
Asthenia	29 (28.4)	41 (36.0)
Dyspnea	29 (28.4)	26 (22.8)
Nausea	27 (26.5)	31 (27.2)
Acne	26 (25.5)	38 (33.3)
Anorexia	24 (23.5)	31 (27.2)
Pain	23 (22.5)	15 (13.2)
Cough increased	22 (21.6)	23 (20.2)
Vomiting	22 (21.6)	21 (18.4)
Dry skin	17 (16.7)	30 (26.3)
Peripheral edema	15 (14.7)	11 (9.6)
Chest pain	14 (13.7)	15 (13.2)
Back pain	14 (13.7)	13 (11.4)
Constipation	13 (12.7)	8 (7.0)
Weight loss	12 (11.8)	12 (10.5)
Pharyngitis	11 (10.8)	16 (14.0)
Pruritus	11 (10.8)	10 (8.8)
Sinusitis	11 (10.8)	4 (3.5)
Abdominal pain	10 (9.8)	14 (12.3)
Fever	8 (7.8)	12 (10.5)
Dehydration	5 (4.9)	13 (11.4)

Drug-related adverse events with an incidence of $\geq 5\%$ in either dose group are presented in **Table 36**.

The most frequent drug-related adverse events experienced by $\geq 10\%$ of patients receiving ZD1839 250 mg/day were diarrhea (48.0%), rash (43.1%), acne (24.5%), dry skin (12.7%), nausea (12.7%), and vomiting (11.8%). With the exception of vomiting, the incidence of these events was lower at the 250-mg/day dose than at the 500-mg/day dose.

The majority of patients receiving ZD1839 250 mg/day who experienced drug-related adverse events had events that were CTC Grades 1 or 2 (67 out of 74 patients; 90.5%). Drug-related adverse events generally occurred for the first time in Treatment Periods

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1 or 2, and the safety profile of ZD1839 did not appear to change with chronic dosing (up to a maximum of nearly 8 months of treatment).

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Table 36: Drug-related adverse events with an incidence of $\geq 5\%$ in trial 39

Drug-related adverse event (COSTART term) ¹	Number of patients	
	250 mg/day (n=102)	500 mg/day (n=114)
Diarrhea	49 (48.0)	76 (66.7)
Rash	44 (43.1)	61 (53.5)
Acne	25 (24.5)	37 (32.5)
Dry skin	13 (12.7)	30 (26.3)
Nausea	13 (12.7)	20 (17.5)
Vomiting	12 (11.8)	10 (8.8)
Pruritus	8 (7.8)	10 (8.8)
Anorexia	7 (6.9)	11 (9.6)
Asthenia	6 (5.9)	5 (4.4)
Weight loss	3 (2.9)	6 (5.3)

¹ A patient may have had more than 1 adverse event.

COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

Adverse events with CTC Grades 3 or 4

Thirteen (12.7%) patients on ZD1839 250-mg/day had CTC Grade 4 adverse events compared to 20 (17.5%) on the 500-mg/day dose. Two (2.0%) patients at the 250-mg/day dose had Grade 4 adverse events that were considered drug related (asthenia and thrombocytopenia) compared to 3 (2.6%) at the 500-mg/day dose (dehydration, lung hemorrhage, and ALT/SGPT increased).

Twenty-eight (27.5%) patients at the 250-mg/day dose had CTC Grade 3 adverse events compared to 33 (28.9%) on the 500-mg/day dose. Five (4.9%) patients at the 250-mg/day dose had Grade 3 adverse events that were considered drug related compared to 17 (14.9%) at the 500-mg/day dose.

Diarrhea and acne were the only drug-related adverse events of CTC Grade 3 or 4 severity with an incidence of $\sim 3\%$ in either dose group (see **Table 37**).

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Table 37: Drug-related adverse events of CTC Grade 3 or 4 in trial 39

Adverse event and CTC grade	Number (%) of patients	
	250 mg/day (n=102)	500 mg/day (n=114)
Asthenia		
Grade 3	1(1.0)	1 (0.9)
Grade 4	1(1.0)	0(0.0)
Diarrhea, Grade 3	1(1.0)	6(5.3)
Gastrointestinal disorder,		
Grade 3	0(0.0)	1(0.9)
Nausea, Grade 3	1(1.0)	1 (0.9)
Rectal disorder, Grade 3	1(1.0)	0(0.0)
Vomiting, Grade 3	1(1.0)	3(2.6)
Thrombocytopenia, Grade 4	1(1.0)	0(0.0)
Dehydration		
Grade 3	0(0.0)	2(1.8)
Grade 4	0(0.0)	1(0.9)
Peripheral edema, Grade 3	1(1.0)	0(0.0)
AST/SGOT increased,		
Grade 3	0(0.0)	2(1.8)
ALT/SGPT increased		
Grade 3	0(0.0)	1 (0.9)
Grade 4	0(0.0)	1 (0.9)
Dyspnea, Grade 3	1(1.0)	0(0.0)
Epistaxis, Grade 3	1(1.0)	0(0.0)
Lung hemorrhage, Grade 4	0(0.0)	1 (0.9)
Acne, Grade 3	0(0.0)	4(3.5)
Pruritus, Grade 3	0(0.0)	1 (0.9)
Rash, Grade 3	0(0.0)	3(2.6)
Scrotal edema, Grade 3	1(1.0)	0(0.0)

Deaths

The number (%) of patients who died during Trial 0039, and the primary cause of death (disease related or adverse event), are summarized in **Table 38**.

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Table 38: Deaths during or 30 days post treatment in trial 39

Category	Number (%) of patients a	
	250 mg/day (n= 102)	500 mg/day (n=114)
Patients who died	22(21.6)	27(23.7)
Patients whose death was considered cancer related a	21 (20.6)	26(22.8)
Patients who had an adverse event that resulted in death	6(5.9)	5(4.4)

a Death reported as cancer related by the investigator. Includes 9 patients who also had an adverse event with an outcome of death.

For the 11 patients who had an adverse event that resulted in death the death was considered cancer related by the investigator for 9 out of 11 of these patients. The remaining 2 patients (2107/0034 and 2107/0035) died of cardiovascular events (arrhythmia and acute myocardial infarction, respectively); both had a history of cardiovascular disease. Only 1 patient (2107/0145; 500 mg/day group) had an adverse event (lung hemorrhage) that led to death that was considered possibly related to ZD1839 by the investigator. This patient's death was also reported as cancer related.

Adverse events leading to withdrawal

The incidence of withdrawals from ZD1839 treatment due to adverse events was lower in the 250-mg/day group (3.9%) than in the 500-mg/day group (9.6%).

One patient (1.0%) in the 250-mg/day group, and 5 patients (4.4%) in the 500-mg/day group, were withdrawn due to adverse events that were considered to be possibly drug related by the investigator. The identification of these patients is presented in **Table 39**. The only drug-related adverse events that led to withdrawal in more than 1 patient were diarrhea, acne, and rash (2 patients each).

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Table 39: Patients who withdrew due to drug-related adverse events in trial 39

Center/patient number	Tumor type	Adverse event	Serious event	CTC grade (yes/no)	Outcome	Days on treatment
250-mg/day group						
2255/0302	Adenocarcinoma	Asthenia	Yes	4	Ongoing	140 a
500-mg/day group						
2044/0182	Squamous	Acne	No	3	Recovered	71
		Rash	No	3	Ongoing	
2102/0071	Adenocarcinoma	Acne	No	3	Ongoing	92
2107/0035	Adenocarcinoma	Diarrhea	No	I	Ongoing	63
2107/0145	Squamous and adenocarcinoma	Lung hemorrhage	Yes	4	Died	11 b
2251/0063	Adenocarcinoma	Abd. pain	No	I	Recovered	14
		Headache	No	I	Recovered	
		Diarrhea	No	I	Recovered	
		Epistaxis	No	I	Recovered	
		Pruritus	No	2	Recovered	
		Rash	No	2	Recovered	

a Reported term progressive neurologic deterioration. Onset of the event occurred on Day 85; the duration of treatment is based on the date of the last dose at the time of data cutoff.

b Onset of the event (patient began coughing up blood) occurred on Day 3; the patient was withdrawn and subsequently died on Day 11.

Eleven patients withdrew because of adverse events that were not considered drug related (including 2 patients who also had drug-related adverse events that led to withdrawal). Among the 11 patients, the only events that led to withdrawal in more than 1 patient were pneumonia (4 patients), dyspnea (3 patients), and apnea (2 patients).

Serious adverse events

Twenty-eight patients (27.5%) at the 250-mg/day dose had at least 1 serious adverse event compared to 27 (23.7%) at the 500-mg/day dose. Of these patients, 4 at the 250-mg/day dose, and 5 at the 500-mg/day dose, had drug-related serious adverse events. Dehydration and asthenia were the only drug-related serious adverse events reported by more than 1 patient.

Identification of patients with drug-related serious adverse events is presented in **Table 40**.

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Table 40: Patients who had drug-related serious adverse events in trial 39

Center/ patient	Tumor type description	Adverse event	CTC grade	Outcome	Withdrawn because of the event (yes/no)	Days on treatment at time of event
250-mg/day group						
2064/0077	Adenocarcinoma	Rectal disorder	3	Recovered	No	115
		Thrombocytopenia	4	Recovered	No	114
		Epistaxis	3	Recovered	No	115
2118/0172	Squamous and adenocarcinoma	Asthenia	3	Ongoing	No	18
2251/0066	Adenocarcinoma	Peripheral edema	3	Recovered	No	91
		Scrotal edema	3	Ongoing	No	91
2255/0302	Adenocarcinoma	Asthenia	4	Ongoing	Yes	85
500-mg/day group						
2090/0047	Adenocarcinoma	Dehydration	4	Ongoing	No	1 day post trt
2090/0220	Adenocarcinoma	Increased AST/SGOT	3	Recovered	No	65
		Increased ALT/SGPT	4	Recovered	No	65
2107/0145	Squamous and adenocarcinoma	Lung hemorrhage	4	Died	Yes	3
2251/0064	Adenocarcinoma	Dehydration	3	Recovered	No	23
2252/0274	Adenocarcinoma	Nausea	3	Ongoing	No	81
		Vomiting	3	Ongoing	No	81
		Dehydration	3	Ongoing	No	81

Phase II Supportive Trial 0016

An overview of adverse events occurring in Trial 0016 is summarized in **Table 41**. Adverse events are reported by the dose of ZD1839 assigned at trial entry.

Table 41: Overview of adverse events in trial 16

Category	Number of patients	
	250 mg/day (n=103)	500 mg/day (n=106)
All adverse events	101(98.1)	106(100)
drug related	88(85.4)	102(96.2)
Deaths		
due to adverse event(s)	4(3.9)	1 (0.9)
due to drug-related adverse event(s)	0(0.0)	1 (0.9)
Withdrawals		
due to adverse event(s)	7(6.8)	12(11.3)
due to drug-related adverse event(s)	2(1.9)	10(9.4)
due to serious adverse event(s)	6(5.8)	6(5.7)
due to drug-related serious adverse event(s)	1(1.0)	4(3.8)
Serious adverse events	21(20.4)	27(25.5)
drug-related	3(2.9)	12 (11.3)
CTC Grade 3 or 4 adverse events	33(32.0)	54(50.9)
drug related	9(8.7)	32(30.2)

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Nearly all patients (99.0%) in Trial 16 had at least 1 adverse event. Those adverse events with an incidence of $\geq 10\%$ in either dose group are presented in **Table 42**.

Table 42: Adverse events with an overall incidence $\geq 10\%$ in trial 16

Adverse event	Number of patients	
	250 mg/day (n=103)	500 mg/day (n=106)
Diarrhea	50(48.5)	71(67.0)
Rash	49(47.6)	74(69.8)
Pruritus	32(31.1)	39(36.8)
Dry skin	30(29.1)	31 (29.2)
Asthenia	26(25.2)	23(21.7)
Nausea	25(24.3)	37(34.9)
Pharyngitis	19(18.4)	25(23.6)
Anorexia	18(17.5)	30(28.3)
ALT/SGPT increased	17(16.5)	26(24.5)
Vomiting	16(15.5)	34(32.1)
AST/SGOT increased	16(15.5)	24(22.6)
Dyspnea	16(15.5)	15(14.2)
Pain	13(12.6)	27(25.5)
Acne	13(12.6)	17(16.0)
Constipation	12(11.7)	14(13.2)
Cough increased	11 (10.7)	13 (12.3)
Weight loss	10(9.7)	17(16.0)
Abdominal pain	10(9.7)	14(13.2)
Conjunctivitis	9(8.7)	13 (12.3)
Stomatitis	9(8.7)	12(11.3)
Fever	8(7.8)	21 (19.8)
Rhinitis	7(6.8)	13(12.3)
Hernaturia	7(6.8)	11(10.4)
Epistaxis	5(4.9)	19(17.9)

Drug-related adverse events in Trial 0016 with an overall incidence of $\geq 5\%$ are presented in **Table 43**. The majority of patients receiving ZD1839 250 mg/day who experienced drug-related events had events that were CTC Grades 1 or 2 (79 out of 88 patients; 89.8%). Drug-related adverse events generally occurred for the first time in Treatment Period 1, and the safety profile of ZD1839 did not appear to change with chronic dosing (up to a maximum of nearly 8 months of treatment).

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Table 43: Drug-related adverse events $\geq 5\%$ in trial 16

Drug-related adverse event	Number of patients	
	250 mg/day (n= 103)	500 mg/day (n=106)
Rash	48(46.6)	73(68.9)
Diarrhea	41 (39.8)	61 (57.5)
Pruritus	31 (30.1)	38(35.8)
Dry skin	28(27.2)	31 (29.2)
Nausea	13(12.6)	25(23.6)
ALT/SGPT increased	13(12.6)	25(23.6)
Acne	13(12.6)	15(14.2)
AST/SGOT increased	11(10.7)	24(22.6)
Pain	10(9.7)	17(16.0)
Anorexia	9(8.7)	20(18.9)
Asthenia	8(7.8)	11 (10.4)
Exfoliative dermatitis	8(7.8)	9(8.5)
Stomatitis	8(7.8)	8(7.5)
Vomiting	6(5.8)	21 (19.8)
Hernaturia	6(5.8)	5(4.7)
Seborrhea	6(5.8)	4(3.8)
Blepharitis	5(4.9)	6(5.7)
Conjunctivitis	4(3.9)	10(9.4)
Nail disorder	4(3.9)	9(8.5)
Abdominal pain	3(2.9)	8(7.5)
Epistaxis	2(1.9)	12(11.3)
Weight loss	2(1.9)	6(5.7)

' A patient may have had more than 1 adverse event.

Adverse events with CTC Grades 3 or 4

Twelve (11.7%) patients at the 250-mg/day dose had CTC Grade 4 adverse events compared to 12 (11.4%) at the 500-mg/day dose. No drug-related CTC Grade 4 events were reported in the 250-mg/day group. Six patients (5.7%) had drug-related CTC Grade 4 adverse events in the 500-mg/day group.

Twenty-one (20.4%) patients at the 250-mg/day dose had CTC Grade 3 adverse events compared to 42 (39.6%) at the 500-mg/day dose. Eight (7.8%) patients at the 250-mg/day dose had drug related CTC Grade 3 events compared to 24 (22.6%) at the 500-mg/day dose.

Diarrhea, ALT/SGPT increased, and rash were the only drug-related adverse events of CTC Grade 3 or 4 severity with an incidence $\sim 3\%$ in either dose group (see **Table 44**).

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Table 44: Drug-related adverse events of CTC Grade 3 or 4 in trial 16

Adverse event and CTC grade	Number of patients	
	250 mg/day (n=103)	500 mg/day (n=106)
Asthenia, Grade 3	0(0.0)	1 (0.9)
Shock, Grade 4	0(0.0)	1 (0.9)
Atrial fibrillation, Grade 3	1(1.0)	0(0.0)
Bundle branch block, Grade 3	1(1.0)	0(0.0)
Deep thrombophlebitis, Grade 4	0(0.0)	1 (0.9)
Anorexia, Grade 3	0(0.0)	1 (0.9)
Constipation, Grade 3	1(1.0)	0(0.0)
Diarrhea, Grade 3	0(0.0)	7(6.6)
Gastrointestinal hemorrhage, Grade 3	0(0.0)	1 (0.9)
Liver function tests abnormal, Grade 3	0(0.0)	1 (0.9)
Melena, Grade 3	0(0.0)	1 (0.9)
Nausea, Grade 3	1(1.0)	1 (0.9)
Anemia		
Grade 3	0(0.0)	1 (0.9)
Grade 4	0(0.0)	2 (1.9)
Alkaline phosphatase increased, Grade 3	1(1.0)	0(0.0)
Dehydration, Grade 3	1(1.0)	0(0.0)
Hypoproteinemia, Grade 3	0(0.0)	1 (0.9)
AST/SGOT increased		
Grade 3	0(0.0)	2(1.9)
Grade 4	0(0.0)	1 (0.9)
ALT/SGPT increased		
Grade 3	2(1.9)	5(4.7)
Grade 4	0(0.0)	1 (0.9)
Dyspnea, Grade 3	0(0.0)	1 (0.9)
Hypoxia, Grade 3	0(0.0)	1 (0.9)
Interstitial pneumonia, Grade 3	0(0.0)	1 (0.9)
Pneumonia		
Grade 3	0(0.0)	1 (0.9)
Grade 4	0(0.0)	1 (0.9)
Acne, Grade 3	0(0.0)	2(1.9)
Exfoliative dermatitis, Grade 3	0(0.0)	2(1.9)
Nail disorder, Grade 3	0(0.0)	1 (0.9)
Pruritus, Grade 3	0(0.0)	1 (0.9)
Rash		
Grade 3	1 (1.0)	6(5.7)
Grade 4	0(0.0)	1 (0.9)
Seborrhea, Grade 3	1 (1.0)	0(0.0)

Deaths

Twenty-three (22.3%) patients in the 250-mg/day group died during treatment or post-treatment (ie, within 30 days after the last dose of ZD1839) compared to 12 (11.3%) in the 500-mg/day group. Four (3.9%) patients in the 250-mg/day group had adverse events with an outcome of death. Three of these deaths were considered cancer related. In addition, 1 (0.9%) patient in the 500mg/day group had an adverse event with an outcome of death. None of these 5 deaths associated with adverse events were considered by the investigator to be possibly related to trial medication. However, for 1 patient (0207/0001), the investigator felt unable to assign causality. On review of this case, an AstraZeneca physician assigned a causality of "drug related". This patient was a 62year-old white woman with advanced NSCLC (adenocarcinoma; Stage IV who was assigned to the 500-mg/day dose. Fifty-nine days after starting trial therapy, she had acute respiratory insufficiency: pneumonia and died 2 days after onset. The adverse event was CTC Grade 4.

Adverse events leading to withdrawal

The incidence of withdrawals from ZD1839 treatment due to adverse events was lower in the 250-mg/day group (6.8%) than in the 500-mg/day group (11.3%).

Two patients (1.9%) in the 250-mg/day group, and 10 patients (9.4%) in the 500-mg/day group, were withdrawn due to adverse events that were considered to be possibly drug related by the investigator. The identification of these patients is presented in **Table 45**. The only drug-related adverse events that led to withdrawal of more than 1 patient were rash, pneumonia, increased ALT/SGPT, and increased AST/SGOT.

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Table 45: Patients who withdrew due to drug-related adverse events in Trial 0016

Center/patient number	Tumor type	Adverse event	Serious (yes/no)	CTC grade	Outcome	Days on treatment
250-mg/day group						
0259/0007	Squamous	Bundle branch block	Yes	3	Ongoing	112
0815/0004	Adenocarcinoma	ALT/SGPT increased	No	3	Resolved	41
500-mg/day group						
0207/0001	Adenocarcinoma	Pneumonia	Yes	4	Died	59
0259/0002	Adenocarcinoma	Diarrhea	No	3	Ongoing	2
		Nausea	No	3	Resolved	2
		Vomiting	No	2	Ongoing	2
		Rash	No	1	Ongoing	10
0259/0005	Adenocarcinoma	Rash	No	1	Ongoing	10
0804/0001	Adenocarcinoma	Liver function tests abnormal	No	3	Ongoing	57
0804/0002	Adenocarcinoma	Pneumonia	Yes	3	Ongoing	87
		Hypoxia	Yes	3	Resolved	88
0805/0002	Adenocarcinoma	Generalized edema	Yes	2	Ongoing	24
		Hypoproteinemia	Yes	3	Ongoing	57
0807/0002	Adenocarcinoma	ALT/SGPT increased	No	4	Resolved	29
		AST/SGOT increased	No	4	Resolved	29
0808/0002	Adenocarcinoma	Deep thrombophlebitis	Yes	4	Ongoing	92
0819/0008	Adenocarcinoma	ALT/SGPT increased	No	3	Ongoing	29
		AST/SGOT increased	No	3	Ongoing	43
0820/0003	Squamous	Rash	No	3	Resolved	7

Serious adverse events

Twenty-one patients (20.4%) at the 250-mg/day dose had at least 1 serious adverse event compared to 27 (25.5%) at the 500-mg/day dose. Of these patients, 3 at the 250-mg/day dose, and 12 at the 500-mg/day dose, had drug-related serious adverse events (**Table 46**).

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Table 46: Patients who had drug-related serious adverse events in trial 16

Center/patient on number	Tumor type	Adverse event grade	CTC because of the adverse event (yes/no)	Outcome treatment at time of event	Withdrawn Days
250-mg/day group					
0207/0003	Adenocarcinoma	Diarrhea	2 Ongoing	No	30
0259/0007	Squamous	Bundle branch block	3 Ongoing	Yes	112
0601/0009	Adenocarcinoma	Dehydration	3 Resolved	No	33
500-mg/day group					
0111/0003	Adenocarcinoma	Asthenia	3 Ongoing	No	14
0205/0002	Adenocarcinoma	Anemia	4 Ongoing	No	26
		GI hemorrhage	3 Ongoing	No	26
		Melena	3 Ongoing	No	26
		Shock	4 Ongoing	No	26
0207/0001	Adenocarcinoma	Pneumonia	4 Died	Yes	59
02511/0001	Adenocarcinoma	Acne	3 Ongoing	No	11
0259/0004	Squamous	Nausea	2 Resolved	No	1
		Vomiting	2 Resolved	No	1
0416/0004	Adenocarcinoma	Diarrhea	3 Resolved	No	59
0601/0010	Undifferentiated	Diarrhea	3 Resolved	No	14
0804/0002	Adenocarcinoma	Pneumonia	3 Ongoing	Yes	87
		Hypoxia	3 Resolved	Yes	88
0805/0002	Adenocarcinoma	Generalized edema	2 Ongoing	Yes	24
		Anemia	3 Ongoing	No	57
		Hypoproteinemia	3 Ongoing	Yes	57
0808/0001	Large cell	Dyspnea	3 Ongoing	No	17
		Interstitial pneumonia	3 Resolved	No	17
0808/0002	Adenocarcinoma	Deep thrombophlebitis	4 Ongoing	Yes	92
0818/0003	Adenocarcinoma	Rash	2 Resolved	No	32

Phase I trials: patients with solid tumors

6.3.1 Overall incidences of adverse events

An overview of adverse events for patients with solid tumors who received ZD 1839 in the Phase I multiple-dose trials (0005, 0011, 0012, 0038, and V- 15-11) is summarized by dose in **Table 47**.

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Table 47: Overview of adverse events in the Phase I multiple-dose trials

Category	Number (%) of patients a				All doses (n=270)
	<225 mg (n=51)	250 mg b (n=75)	500 mg c (n=72)	>525 mg (n=72)	
All adverse events	51 (100)	74 (98.7)	72 (100)	71 (98.6)	268 (99.3)
drug related	28 (54.9)	58 (77.3)	65 (90.3)	68 (94.4)	219 (81.1)
Deaths					
due to adverse event(s)	2 (3.9)	8 (10.7)	3 (4.2)	1 (1.4)	14 (5.2)
due to drug-related adverse event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawals					
due to adverse event(s)	5 (9.8)	7 (9.3)	7 (9.7)	19 (26.4)	38 (14.1)
due to drug-related adverse event(s)	1 (2.0)	2 (2.7)	3 (4.2)	18 (25.0)	24 (8.9)
due to serious adverse event(s)	3 (5.9)	5 (6.7)	4 (5.6)	8 (11.1)	20 (7.4)
due to drug-related serious adverse	0 (0.0)	1 (1.3)	1 (1.4)	7 (9.7)	9 (3.3)
Serious adverse events	15 (29.4)	22 (29.3)	13 (18.1)	29 (40.3)	79 (29.3)
drug-related	1 (2.0)	4 (5.3)	1 (1.4)	14 (19.4)	20 (7.4)
CTC Grade 3 or 4 adverse events	22 (43.1)	34 (45.3)	25 (34.7)	37 (51.4)	118 (43.7)
drug related	1 (2.0)	5 (6.7)	7 (9.7)	26 (36.1)	39 (14.4)

a Patients may appear in more than 1 category of adverse event.

b Including doses between 225 mg and 300 mg, inclusive.

c Including doses between 400 mg and 525 mg, inclusive.

Adverse events

Nearly all patients (99.3%) in the Phase I multiple-dose trials experienced at least 1 adverse event. Adverse events with an overall incidence $\geq 10\%$ are presented by dose category in **Table 48**.

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Table 48: Adverse events $\geq 10\%$ in the Phase I multiple-dose trials

Adverse event	Number (%) of patients a				
	<225 mg (n=51)	250 mg b (n=75)	500mg c (n=72)	>525 mg (n=72)	All doses (n=270)
Diarrhea	18(35.3)	34(45.3)	42(58.3)	58(80.6)	152(56.3)
Rash	14(27.5)	27(36.0)	35(48.6)	45(62.5)	121 (44.8)
Nausea	18(35.3)	19(25.3)	26(36.1)	32(44.4)	95(35.2)
Asthenia	13(25.5)	26(34.7)	23 (31.9)	26(36.1)	88(32.6)
Vomiting	11(21.6)	22(29.3)	21(29.2)	23(31.9)	77(28.5)
Anorexia	10(19.6)	18(24.0)	20(27.8)	23(31.9)	71 (26.3)
Dry skin	4(7.8)	14(18.7)	19(26.4)	23(31.9)	60(22.2)
Acne	4(7.8)	16(21.3)	19(26.4)	17(23.6)	56(20.7)
Abdominal pain	15(29.4)	5(6.7)	10(13.9)	21 (29.2)	51(18.9)
Cough increased	10(19.6)	15(20.0)	12(16.7)	14(19.4)	51(18.9)
Dyspnea	8(15.7)	15(20.0)	15(20.8)	11 (15.3)	49(18.1)
Headache	12(23.5)	13(17.3)	13 (18.1)	8(11.1)	46(17.0)
Pharyngitis	8(15.7)	12(16.0)	8(11.1)	14(19.4)	42(15.6)
Constipation	12(23.5)	12(16.0)	11 (15.3)	5(6.9)	40(14.8)
Pain	10(19.6)	8(10.7)	14(19.4)	8(11.1)	40(14.8)
Conjunctivitis	9(17.6)	10(13.3)	8 (11.1)	12(16.7)	39(14.4)
Dry mouth	5(9.8)	9(12.0)	5(6.9)	19(26.4)	38(14.1)
Pruritus	4(7.8)	5(6.7)	12(16.7)	16(22.2)	37(13.7)
Somnolence	10(19.6)	9(12.0)	9(12.5)	9(12.5)	37(13.7)
AST/SGOT increased	7(13.7)	8(10.7)	12(16.7)	7(9.7)	34(12.6)
Fever	9(17.6)	10(13.3)	3(4.2)	9(12.5)	31(11.5)
ALT/SGPT increased	5(9.8)	7(9.3)	9(12.5)	8(11.1)	29(10.7)
Anemia	4(7.8)	9(12.0)	8 (11.1)	7(9.7)	28(10.4)
Back pain	3(5.9)	8(10.7)	6(8.3)	10(13.9)	27(10.0)

a patients may have had more than 1 adverse event.

b Including doses between 225 mg and 300 mg, inclusive.

c Including doses between 400 mg and 525 mg, inclusive.

Dose-limiting toxicities

In Trials 0005 and V- 15-11, dose escalation was to proceed up to 925 mg/day unless there was dose limiting toxicity. Dose escalation ceased at 700 mg/day in both of these trials; in Trial 0005, three patients experienced drug-related CTC Grade 3 or 4 diarrhea at this dose level, and in Trial V- 15 -11, two patients experienced CTC Grade 3 diarrhea and increased ALT/SGPT at this dose level (**see Table 49**).

In Trials 0011 and 0012, dose escalation was to proceed up to 1000 mg/day unless dose-limiting toxicities were recorded. In Trial 0011, dose-limiting toxicities were experienced in the first 28-day treatment period by 3 patients receiving ZD1839 800 mg; the events experienced were diarrhea, diarrhea and pruritus, and conjunctivitis and rash (**see Table 49**). In Trial 0012, dose escalation proceeded up to the maximum permitted dose level of 1000 mg/day. At this dose level, 5 patients experienced dose-limiting toxicities which, for 4 of these patients, included Grade 3 diarrhea (**see Table 49**).

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Table 49: Dose limiting toxicities in the Phase I dose-escalating trials

Trial	ZD1839 dose (mg)	Center/ Patient	Tumor type	Adverse event	CTC grade	
0005	400	0001/0061	Ovarian	ALT increased	3	
				AST increased	4	
	525	0004/0071	Esophageal	Acne	3	
	700	0001/0081	Ovarian	Diarrhea	4	
		0002/0083	NSCLC	Diarrhea	3	
		0004/0081	Ovarian	Vomiting	3	
				Abdominal pain	3	
				Diarrhea	3	
	0011	150	0001/0001	NSCLC	GGT increased	3
800		0002/0105	NSCLC	Diarrhea	3	
		0004/0107	Colorectal	Diarrhea	3	
				Pruritus	3	
		0008/0101	NSCLC	Conjunctivitis	2	
				Rash	3	
1000		0004/0121	NSCLC	Diarrhea	3	
		0005/0123	Prostate	Diarrhea	3	
		0008/0122	NSCLC	Dehydration	3	
				Urticaria	3	
				Diarrhea	3	
				Rash	3	
0012		225	0011/0027	Prostate	Nausea	3
		300	0010/0054	Prostate	Diarrhea	3
		400	0005/0065	Colorectal	Rash	3
			0011/0061	Ovarian	Pain	3
	Pruritus				3	
				Depression	3	
				Diarrhea	3	
	600	0008/0090	Ovarian	Diarrhea	3	
		0011/0081	Head & neck	Somnolence	3	
		800	0001/0110	Colorectal	Asthenia	4
		0005/0108	Colorectal	Diarrhea	3	
		1000	0001/0123	Ovarian	Diarrhea	3
	Somnolence				3	
	V-15-11 700				Hematemesis	3
					Hypokalemia	3
					Acne	3
					Diarrhea	3
					Diarrhea	3
Dehydration					3	
Diarrhea					3	
Somnolence					3	
ALT increased					3	
Diarrhea					3	

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Drug-related adverse events

A total of 219 patients (81.1%) had at least 1 adverse event that was attributed to trial medication. Drug-related adverse events with an overall incidence of $\geq 5\%$ are presented in **Table 50**.

The most frequent drug-related adverse events were diarrhea, rash, acne, dry skin, nausea, pruritus, and vomiting. These are similar to the most frequent drug-related adverse events reported in the Phase II trials.

Table 50: Drug-related adverse events ($\geq 5\%$) in the Phase I multiple-dose trials

Drug-related adverse event Number (%) of patients a

	<225 mg (n=51)	250 mg b (n=75)	500 mg c (n=72)	>525 mg d (n=72)	All doses (n=270)
Diarrhea	6(11.8)	24(32.0)	31 (43.1)	56(77.8)	117(43.3)
Rash	8(15.7)	23(30.7)	34(47.2)	45(62.5)	110(40.7)
Acne	4(7.8)	15(20.0)	18(25.0)	17(23.6)	54(20.0)
Dry skin	1 (2.0)	12(16.0)	16(22.2)	22(30.6)	51 (18.9)
Nausea	1 (2.0)	7(9.3)	12(16.7)	22(30.6)	42(15.6)
Pruritus	2(3.9)	3(4.0)	9(12.5)	15(20.8)	29(10.7)
Vomiting	2(3.9)	4(5.3)	5(6.9)	17(23.6)	28(10.4)
Asthenia	1 (2.0)	5(6.7)	6(8.3)	11 (15.3)	23 (8.5)
Dry mouth	2(3.9)	4(5.3)	2(2.8)	15(20.8)	23(8.5)
Anorexia	1 (2.0)	2(2.7)	5(6.9)	11 (15.3)	19(7.0)
AST/SGOT increased	1(2.0)	4(5.3)	7(9.7)	5(6.9)	17(6.3)
ALT/SGPT increased	1(2.0)	4(5.3)	5(6.9)	5(6.9)	15(5.6)

a patients may have had more than 1 drug-related adverse event.

b Including doses between 225 mg and 300 mg, inclusive.

c including doses between 400 mg and 525 mg, inclusive.

d doses of ZD1839 of >525 mg

Adverse events with CTC grades 3 or 4

Overall, 118 patients (43.7%) had CTC Grade 3 or 4 adverse events. Thirty-nine patients (14.4%) had Grade 3 or 4 events that were considered drug related, and these occurred with increasing frequency with increasing dose. As in Trial 39, diarrhea was the only drug-related adverse event of CTC Grade ≥ 3 severity with an incidence of $\geq 3\%$ in the total population. Seventeen out of 19 patients who experienced drug-related CTC Grade 3 or 4 diarrhea were receiving mg/day.

Deaths

A total of 14 out of 270 (5.2%) patients had adverse events in the Phase I multiple-dose trials that had an outcome of death. These patients were distributed across doses from 150 mg/day to 800 mg/day, and none of these events were considered by the investigators to be possibly related to ZD1839.

Withdrawals due to adverse events

A total of 38 out of 270 (14.1%) patients withdrew from ZD1839 therapy due to one or more adverse events. In 24 of these patients, the adverse events were considered to be possibly drug related; in 16 cases, withdrawal was due to gastrointestinal symptoms with 12 cases due to drug related diarrhea.

Serious adverse events

Seventy-nine (29.3%) patients experienced at least 1 serious adverse event. The commonest serious adverse events reported ($\geq 2\%$; 6 or more patients) were abdominal pain (4.4%), dyspnea (3.7%), dehydration (3.0%), asthenia (2.6%), diarrhea (2.6%), and anemia (2.2%). Twenty (7.4%) patients experienced drug-related serious adverse events. Only 4 of these patients were receiving doses ≤ 525 mg/day.

All drug-related adverse events with a frequency $\geq 5\%$ in any of the Phase II and I multiple-dose patient trials is summarized in **Table 51**.

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Table 51: Drug-related adverse events in the Phase II and I multiple-dose patient trials

Drug-related AE	Phase II Trial 0039		Number (%) of patients Phase II Trial 0016		Phase I trials	
	250 mg/day (n=102)	500 mg/day (n=114)	250 mg/day (n=103)	500 mg/day (n=106)	225 to 300 mg/day (n=75)	400 to 525 (n=72)
Diarrhea	49(48.0)	76(66.7)	41 (39.8)	61 (57.5)	24(32.0)	31 (43.1)
Rash	44(43.1)	61 (53.5)	48(46.6)	73(68.9)	23(30.7)	34(47.2)
Acne	25(24.5)	37(32.5)	13 (12.6)	15(14.2)	15(20.0)	18(25.0)
Dry skin	13(12.7)	30(26.3)	28(27.2)	31 (29.2)	12(16.0)	16(22.2)
Nausea	13(12.7)	20(17.5)	13 (12.6)	25(23.6)	7(9.3)	12(16.7)
Vomiting	12(11.8)	10(8.8)	6(5.8)	21 (19.8)	4(5.3)	5(6.9)
Pruritus	8(7.8)	10(8.8)	31 (30.1)	38(35.8)	3(4.0)	9(12.5)
Anorexia	7(6.9)	11(9.6)	9(8.7)	20(18.9)	2(2.7)	5(6.9)
Asthenia	6(5.9)	5(4.4)	8(7.8)	11(10.4)	5(6.7)	6(8.3)
Nail disorder	4(3.9)	3(2.6)	4(3.9)	9(8.5)	1 (1.3)	1 (1.4)
Exfol. Dermatitis	4(3.9)	1 (0.9)	8(7.8)	9(8.5)	3(4.0)	3(4.2)
Weight loss	3(2.9)	6(5.3)	2(1.9)	6(5.7)	0(0.0)	1(1.4)
Abdominal pain	3(2.9)	5(4.4)	3(2.9)	8(7.5)	2(2.7)	3(4.2)
Epistaxis	2(2.0)	3(2.6)	2(1.9)	12(11.3)	0(0.0)	0(0.0)
Dry mouth	2(2.0)	3 (2.6)	4(3.9)	2(1.9)	4(5.3)	2(2.8)
Pain	2(2.0)	1(0.9)	10(9.7)	17(16.0)	1 (1.3)	1(1.4)
ALT increased	1 (1.0)	3 (2.6)	13(12.6)	25(23.6)	4(5.3)	5(6.9)
AST increased	1 (1.0)	3(2.6)	11 (10.7)	24(22.6)	4(5.3)	7(9.7)
Conjunctivitis	1(1.0)	3(2.6)	4(3.9)	10(9.4)	1(1.3)	4(5.6)
Blepharitis	1(1.0)	1(0.9)	5(4.9)	6(5.7)	0(0.0)	0(0.0)
Taste perversion	0(0.0)	5(4.4)	1 (1.0)	5(4.7)	2(2.7)	5(6.9)
Stomatitis	0(0.0)	3(2.6)	8 (7.8)	8(7.5)	1 (1.3)	1(1.4)
Seborrhea	0(0.0)	0(0.0)	6(5.8)	4(3.8)	0(0.0)	2(2.8)
Hematuria	0(0.0)	0(0.0)	6(5.8)	4(4.7)	1 (1.3)	2(2.8)
LDH increased	0(0.0)	0(0.0)	1 (1.0)	1(0.9)	4(5.3)	1(1.4)

The incidence of withdrawals due to drug-related adverse events was low across the ZD1839 clinical program especially for patients receiving doses of 250 mg/day or similar; 3 out of 205 (1.5%) patients who received ZD1839 250 mg/day in the Phase II trials were withdrawn due to drug-related adverse events (asthenia, bundle branch block, and increased ALT/SGPT), and 3 out of 126 (2.4%) patients in the Phase I multiple-dose trials receiving doses of ≥ 300 mg/day were withdrawn due to drug-related adverse events (anorexia, nausea, and diarrhea).

7.4 Adequacy of Safety testing

Safety testing was adequate.

7.5 Summary of Critical Safety Findings

Skin

Phase I patients with solid tumors

In the Phase I multiple dose trials in 270 patients with solid tumors, dose related toxicities to the skin have been consistently observed. 192 patients (71.1%) reported adverse events. The most common of these events were rash (44.8%), acne (20.7%), dry skin (22.2%), and pruritus (13.7%). The incidence and severity of skin events in these trials increased with escalating dose and was a dose limiting toxicity in some patients. Patients with rash frequently had associated reports of dry skin, acne, pruritus, and other skin symptoms.

Seven patients experienced drug-related dose-limiting skin toxicity (CTC grade 3); pruritus (n=2 at 400 mg/day and 800 mg/day respectively), acne (n=2, 525 mg/day and 1000 mg/day, respectively), rash (n=2, 400 mg/day and 800 mg/day respectively) and one patient had urticaria plus rash (1000 mg/day).

Fewer events of skin toxicity were reported at doses = 500 mg/day than at doses >500 mg/day. Skin events of rash, acne, dry skin and pruritus were mild, predominantly CTC grade 1 or 2 and generally resolved during the treatment period or following cessation of therapy). Eleven patients reported 15 drug-related skin events of CTC grade 3. None were reported at <225 mg dose level, only 1 patient experienced CTC grade 3 rash at the nominal 250 mg dose level (0011/0002/0044, 300 mg), 1 event each of acne, pruritus and rash were reported at the 500 mg dose level and 11 events were reported at the >525 mg level. (2 acne, 1 dry skin, 1 hair disorder [abnormal lashes], 1 pruritus, 5 rash, and 1 urticaria). Three patients withdrew from ZD1839 due to acne (525 mg/day), rash (one patient receiving 400 mg and one, 800 mg/day) and hair disorder (800 mg/day).

Four patients (1.5%) reported urticaria in these Phase I multiple dose trials (1 at 150 mg/day [CTC grade 2], 1 at 500 mg/day [CTC grade 1] and 2 at 1000 mg/day [CTC grades 1 and 3]). With the exception of 1 patient (150 mg/day) the events were considered drug-related. The onset of the events occurred on days 29, 4, 1, and 5 for the patients receiving 150 mg/day, 500 mg/day and the 2 patients on 1000 mg/day, respectively. None of the events were considered serious and no patients were withdrawn due to urticaria.

The frequency of skin adverse events by CTC grade in the Phase I multiple-dose trials is shown in **Table 52**.

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Table 52: Skin toxicity by CTC grade in the Phase I multiple-dose trials

Adverse event	CTC grade	Number (%) of patients				
		<225 mg (n=51)	250 mg (n=75)	500 mg (n=72)	>525 mg (n=72)	All doses (n=270)
Rash	1	12(23.5)	19(25.3)	24(33.3)	22(30.6)	77(28.5)
	2	2(3.9)	7(9.3)	10(13.9)	18(25.0)	37(13.7)
	3	0(0)	1(1.3)	1(1.4)	5(6.9)	7(2.6)
Acne	1	2(3.9)	14(18.7)	12(16.7)	7(9.7)	35(13.0)
	2	2(3.9)	2(2.7)	6(8.3)	8(11.1)	18(6.7)
	3	0(0)	0(0)	1(1.4)	2(2.8)	3(1.1)
Pruritus	1	4(7.8)	4(5.3)	8(11.1)	9(12.5)	25(9.3)
	2	0(0)	1(1.3)	3(4.2)	6(8.3)	10(3.7)
	3	0(0)	0(0)	1(1.4)	1(1.4)	2(0.7)
Dry Skin	1	4(7.8)	14(18.7)	18(25.0)	19(26.4)	55(20.4)
	2	0(0)	0(0)	1(1.4)	3(4.2)	4(1.5)
	3	0(0)	0(0)	0(0)	1(1.4)	1(0.4)

Phase II monotherapy trials

In the Phase II pivotal Trial 39 and supportive Trial 16 where 205 patients received 250 mg/day and 220 patients had 500 mg/day ZD1839, 323 patients (75.3%) experienced skin events (66.8 % at 250 mg/day and 84.5% at 500 mg/day). Rash (55.3%), acne (22.1%), dry skin (25.4%), pruritus (21.6%) were the most common events reported. Other reported terms relating to rash were, vesiculobullous rash (1.4%), pustular rash (0.5%), and ichthyosis (0.9%). Patients with rash frequently had associated reports of dry skin, acne, pruritus or other skin symptoms eg, exfoliative dermatitis commonly described as desquamation (5.4%). Two hundred -and- seventy-five patients had at least one episode of rash or acne. Seventy-three patients reported rash and pruritus, 51 patients had acne plus rash, and 22 patients had acne plus pruritus.

Skin adverse events by CTC grade in the Phase II trials is presented in **Table 53**.

Table 53: Frequency of skin adverse events by CTC grade in the Phase II trials

Adverse event	CTC grade	ZD1839 Treatment	
		250 mg (n=205)	500 mg (n=220)
Acne	1	30(14.6)	27(12.3)
	2	9(4.4)	22(10.0)
	3	0(0)	6(2.7)
Dry Skin	1	43(21.0)	50(22.7)
	2	4(2.0)	11(5.0)
Pruritus	1	36(17.6)	41(18.6)
	2	7(3.4)	6(2.7)
	3	0(0)	2(0.9)
Rash	1	71(34.6)	74(33.6)
	2	26(12.7)	53(24.1)
	3	1(0.5)	9(4.1)
	4	0(0)	1(0.5)

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Rash

In 192 patients overall (81.7%) the rash first occurred during the first treatment period; in 32 patients (13.6%) the rash began during treatment periods 2 or 3, and 11 patients (4.7%) first had rash during treatment period 4 or beyond. Four patients in the 500 mg/day ZD1839 group were withdrawn from the trial due to skin rash. There were no withdrawals due to rash in the 250 mg/day group.

Acne

A total of 94 patients (22.1 %) had adverse events of acne (19.0% at 250 mg/day and 25.0% at 500 mg/day). In the majority of patients (74.5%, 70/94 events) the acne occurred during the first treatment period. Two patients at the 500mg/day dose were withdrawn from the study due to CTC grade 3 drug-related acne. No patients were withdrawn due to acne in the 250 mg/day group. In the majority of patients with acne (55.3%) the event was documented to have resolved (51.3% at 250 mg /day and 58.2% at 500 mg/day) either during the treatment period or following cessation of therapy. In 42 patients the acne was reported to be 'ongoing'. The majority of these ongoing events are CTC grade 1 (66.7%) and 14 patients are still ongoing in the trial hence resolution of the event is still possible.

For rashes and acne that did not resolve or improve spontaneously a variety of agents were used to manage the skin symptoms, seen during treatment. These included steroid creams, either topical or systemic antibiotics, topical or systemic anti-histamines and occasionally retinoid creams. The successfulness of these agents in treating the skin conditions has varied between patients, with each agent showing some efficacy but not across all patients.

Pruritus

A total of 92 patients (21.6%) had adverse events of pruritus (21 % at 250 mg/day and 22.3% at 500 mg/day). In the majority of patients (58.7%, 54/92 patients) the pruritus occurred during the first treatment period. One patient receiving 500 mg/day ZD1839 was withdrawn from the trial due to CTC grade 2 pruritus and rash, both events were considered drug-related. The majority (59.8%) of the events were documented to have resolved either during the treatment period or following cessation of therapy (51.2% at 250 mg/day and 67.3% at 500 mg/day). Of the 92 patients with pruritus, 80 were reported to have had rash and/or acne.

Dry Skin

A total of 108 patients (25.4%) had adverse events of dry skin. Sixty-nine of the 108 patients (63.9%) had the first occurrence of dry skin during the first treatment period. There were no patients withdrawn from the trial due to dry skin. The majority (52.8%) of the events were documented to have resolved (55.3% at 250 mg/day and 50.8% at 500 mg/day) either during the treatment period or following cessation of therapy. Of the 108 patients with dry skin, 85 patients were reported to have had rash and or acne.

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Nail Disorders

A total of 26 patients across both trials (6.1 %) had 29 events reported which were termed nail disorders (9 patients at 250 mg/day and 17 patients at 500 mg/day). These disorders included paronychia (11), ingrown nails (6), nail changes (4), breaking nail (2), onycholysis (2), nail ridging (1), finger (1) or nail (1) discoloration and nail loss (1). Events for 20 of these patients (3.9% at 250 mg/day and 5.5% at 500 mg/day) were considered possibly related to ZD1839. One patient at the 500mg/day dose had a grade 3 paronychia that occurred on day 12 of treatment and resolved after 92 days. Of the remaining patients, 14 had CTC grade 1 events (2.4% at 250 mg/day and 4.1 % at 500 mg/day) and 11 had CTC grade 2 (2.0% at 250 mg/day and 3.2% at 500 mg/day). None of these events was serious and the majority of these events resolved.

Other Skin Disorders

Toxic epidermal necrolysis (CTC grade 4) and erythema multiforme (CTC Grade unknown) occurred in 1 patient each. These are from a database of greater than 8000 patients exposed to ZD1839.

Ophthalmologic Toxicity

Phase I multiple dose ranging studies

In the Phase I multiple dose trials in patients with solid tumors, ophthalmic monitoring was performed every 2 weeks and included visual acuity, slit-lamp examination with fluorescein and Rose Bengal staining, lid eversion and Schirmer's test.

Baseline findings were seen at all dose levels in 181 patients (67%). During the trial new ophthalmology findings were reported in 122 patients. 68 patients from trials 0005, 0011 and 0012 experienced decreased tear production (measured by Schirmer's test). Data from over 837 routine slit lamp examinations revealed no identifiable trend in abnormalities. The ophthalmological data observed were thought to represent variance within a normal population, and were not believed to be related to trial treatment. Of significance the intensive ophthalmological monitoring did not reveal any findings representative of those detected in the pre-clinical studies eg, diffuse corneal translucency and corneal atrophy.

The number of patients with ocular adverse events, by dose, from Phase I trials is presented in **Table 54**.

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Table 54: Ocular adverse events by dose: patients from Phase I trials

Adverse event	Number (%) of patients				All patients (n=270)
	ZD1839 <225 mg/day (n=51)	ZD1839 250 mg/day (n=75)	ZD1839 500 mg/day (n=72)	ZD1839 >500 mg/day (n=72)	
Total	18(35.3)	22(29.3)	19(26.4)	26(36.1)	85(31.5)
Abnormal vision	1 (2.0)	0(0)	0(0)	0(0)	1 (0.4)
Ambylopia	5(9.8)	8(10.7)	1 (1.4)	0(0)	14(5.2)
Blepharitis	3(5.9)	0(0)	4(5.6)	1(1.4)	8(3.0)
Blindness	0(0)	1 (1.3)	0(0)	0(0)	1 (0.4)
Cataract specified	0(0)	0(0)	0(0)	1(1.4)	1(0.4)
Conjunctivitis	9(17.6)	10(13.3)	8(11.1)	12(16.7)	39(14.4)
Corneal lesion	0(0)	0(0)	2(2.8)	2 (18)	4(1.5)
Comeal opacity	1 (2.0)	1 (1.3)	0(0)	0(0)	2(0.7)
Corneal ulcer	0(0)	0(0)	2(2.8)	2(2.8)	4(1.5)
Dry eyes	3 (5.9)	4(5.3)	2(2.8)	11 (15.3)	20(7.4)
Eye disorder	3 (5.9)	3(4.0)	0(0)	3(4.2)	9(3.3)
Eye hemorrhage	0(0)	2(2.7)	0(0)	1(1.4)	3(1.1)
Eye pain	2(3.9)	0(0)	2(2.8)	0(0)	4(1.5)
Glaucoma	0(0)	0(0)	1 (1.4)	0(0)	1 (0.4)
Keratoconjunctivitis	0(0)	1(1.3)	0(0)	0(0)	1 (0.4)
Keratitis	1 (2.0)	0(0)	0(0)	2(2.8)	3 (1.1)
Lacrimation disorder	1 (2.0)	0(0)	1 (1.4)	0(0)	2(0.7)
Photophobia	1 (2.0)	1(1.3)	0(0)	0(0)	2(0.7)
Retinal disorder	0(0)	0(0)	0(0)	1 (1.4)	1(0.4)
Uveitis	1 (2.0)	0(0)	0(0)	0(0)	1 (0.4)
Visual field defect	0(0)	0(0)	1(1.4)	0(0)	1(0.4)
Vitreous disorder	0(0)	1 (1.3)	0(0)	0(0)	1(0.4)

An external Ophthalmology Advisory Board, consisting of 4 international, independent ophthalmologists reviewed the ophthalmological monitoring results. This review revealed no evidence of any consistent or drug-related ophthalmologic toxicity. The significant ocular adverse events reported of corneal ulcer occurred at higher doses than is currently being recommended. Even so these events were in the most part related to aberrant eyelashes and associated with symptoms of pain or discomfort. The corneal ulcers healed rapidly once lashes had been removed.

The advice from the Ophthalmology Advisory Board, in the absence of any consistent or significant ocular toxicity from the Phase I data, was that for the Phase II studies at doses of 250 mg and 500 mg/day:

- The inclusion/exclusion criteria could be relaxed (eg, concomitant medications, contact lens wear, concurrent eye disorders)
- The level of monitoring could be substantially reduced as any potential ocular safety signals had been associated with easily recognized symptoms
- Investigators and patients should be alerted to the value of eyelid awareness

Phase II monotherapy trials

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In the 2 Phase II trials, complete ophthalmologic evaluations, including slit lamp examination, were performed in a minority of patients (based on phase I findings) at baseline and at trial completion or early withdrawal from the trial (at the end of treatment).

In trial 0039 only 37 (17.1%) patients had ophthalmological assessments at baseline and at either withdrawal or another post baseline visit. One patient had visual impairment noted at withdrawal but not at baseline, 3 patients had hyperemia in 1 or both eyes post baseline, and in 5 patients fluorescein staining in one or both eyes was noted post baseline. Schirmer's test was only performed at baseline in this trial.

In trial 0016, baseline ophthalmology findings were seen in 49 patients (23.4%). New findings were recorded in 38 (18.2%) patients and 78 patients (37%) experienced decreased tear production from baseline, during the trial. The decreased tear production was minimal (<5mm) in most cases and was offset by an increase in tear production in 30 (14.3%) patients.

Changes from baseline in ophthalmological evaluations in these two trials, were thought to represent variance within a normal population, to have no clinical significance and were not attributed by the investigator to be related to trial treatment.

The majority of the events were CTC grade 1 (78/102 [76.5%]) or CTC grade 2 (22/102 [21.6%]). In only 2 patients (2/102 [1.96%]) were the eye events reported as CTC grade 3; these were a serious event of cataract considered not related to trial treatment and a corneal ulcer also considered not drug-related.

Results from the ophthalmological monitoring revealed no evidence of any consistent or drug-related ophthalmologic toxicity in these trials. Although 24% of patients from these 2 monotherapy trials experienced eye symptoms/events, the events were frequently mild (CTC 1) and there was only 2 CTC grade 3 events, both of which were considered unrelated to trial therapy. The corneal erosions/ulcers were reversible and sometimes associated with aberrant eyelash growth. Only 1 of the corneal ulcers occurred at the 250 mg/day dose.

In summary, results from the comprehensive ophthalmology monitoring, including over 1500 slit lamp examinations, obtained from the Phase I/II trials did not reveal any asymptomatic findings representative of those seen in the pre-clinical studies. No evidence of any consistent or drug-related ophthalmologic toxicity was observed in these trials. There is no evidence to suggest a need for any recommendations or precautions for future use of ZD1839 beyond patients being aware that they should seek advice should they develop any eye symptoms.

Gastrointestinal Toxicity

Phase I patients with solid tumors

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In the Phase I multiple dose trials in 270 patients with solid tumors, dose-related toxicities to the gastrointestinal system have been consistently observed. Gastrointestinal adverse events were reported by 221 patients (81.9%). The most common of these events were diarrhea (56.3%), nausea (35.2%), vomiting (28.5%) and anorexia (26.3%); the majority of which were CTC grade 1 or 2.

Table 55 presents the frequency of gastrointestinal events by CTC grade in the Phase I multiple dose trials. No drug-related CTC grade 3 or 4 events of stomatitis or anorexia were reported during the Phase I trials.

Table 55: Gastrointestinal events by CTC grade in Phase I multiple-dose trials

Adverse event		CTC gradeNumber (%) of patients				
(COSTART term)		<225 mg (n=51)	250 mg (n=75)	500 mg (n=72)	>525 mg (n=72)	All doses (n=270)
Diarrhea	1	15(29.4)	26(34.7)	30(41.7)	23 (31.9)	94(34.8)
	2	3(5.9)	6(8.0)	12(16.7)	18(25.0)	39(14.4)
	3	0(0)	2(2.7)	0(0)	16(22.2)	18(6.7)
	4	0(0)	0(0)	0(0)	1(1.4)	1(0.4)
Nausea	1	13(25.5)	10(13.3)	17(23.6)	21 (29.2)	61 (22.6)
	2	5(9.8)	7(9.3)	9(12.5)	9(12.5)	30(11.1)
	3	0(0)	2(2.7)	0(0)	1(1.4)	3(1.1)
	4	0(0)	0(0)	0(0)	1(1.4)	1(0.4)
Vomiting	1	10(19.6)	16(21.3)	13(18.1)	13 (18.1)	52(19.3)
	2	1 (2.0)	6(8.0)	8(11.1)	8(11.1)	23(8.5)
	3	0(0)	0(0)	0(0)	1 (1.4)	1 (0.4)
	4	0(0)	0(0)	0(0)	1(1.4)	1(0.4)
Anorexia	1	7(13.7)	15(20.0)	13(18.1)	18(25.0)	53(19.6)
	2	2(3.9)	1 (1.3)	6(8.3)	5(6.9)	14(5.2)
	3	0(0)	1 (1.3)	1(1.4)	0(0)	2(0.7)
	4	1 (2.0)	1 (1.3)	0(0)	0(0)	2(0.7)
Stomatitis	1	0(0)	2(2.7)	7(9.8)	5(6.9)	14(5.5)
	2	1 (2.0)	0(0)	1(1.4)	3(4.2)	5(1.9)
	3	0(0)	1(1.3)	0(0)	1 (1.4)	2(0.7)

Phase II monotherapy trials

Similar to the phase I trials the phase II trials observed similar gastrointestinal toxicity. In the majority of patients with GI toxicity the adverse event first was noted during treatment period 1 (**Table 56**).

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Table 56: Gastrointestinal adverse events by CTC grade in the Phase II trials

Adverse event a,c	CTC grade	ZD1839 Treatment	
		250 mg (n=205)	500 mg (n=220)
Anorexia	1	28(13.7)	36(16.4)
	2	10(4.9)	22(10.0)
	3	4(2.0)	2(0.9)
	NR	0(0)	1(0.5)
Diarrhea	1	87(42.4)	102(46.4)
	2	19(9.3)	39(17.7)
	3	2(1.0)	15(6.8)
Nausea	1	37(18.0)	45(20.5)
	2	11(5.4)	20 (9.1)
	3	4(2.0)	3(1.4)
Vomiting	1	26(12.7)	36(16.4)
	2	8(3.9)	15(6.8)
	3	3 (1.5)	4(1.8)
	4	1(0.5)	0(0)
Stomatitis b	1	11 (5.4)	21(9.5)
	2	1(0.5)	3(0.7)
	3	0(0)	1(0.5)

a COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

b Stomatitis includes COSTART terms of stomatitis, mouth ulceration and aphthous stomatitis.

NR Not recorded.

c In the Phase II trials diarrhea was the most commonly reported adverse event (52.7% at 250 mg/day; 70.9% at 500 mg/day), the majority of which was CTC grade 1. There were only 2 CTC grade 3 diarrheas at the 250 mg/day dose. No patients withdrew from treatment due to a gastrointestinal event at the 250 mg/day dose.

Electrocardiograms

Phase I multiple dose ranging studies

In the Phase I trials (trials 5, 11 and 12) patients with a P-R interval of greater than 217 msec or a previous history of clinically significant cardiac dysrhythmia, any degree of atrio-ventricular block or other severe cardiac disease were excluded. All patients had a 12-lead ECG at screening, between 5 and 7 hours after the first dose, followed by weekly (trial 5) or 2-weekly (trials 11 and 12) tracings throughout the study period. A total of 1642 ECGs were recorded from the 221 patients participating in these Phase I trials. Review of data from these patients, did not suggest any significant or consistent findings. In particular, there was no indication of PR prolongation and there were no signals of QT prolongation recognized.

Of the 221 patients in Trials 5, 11 and 12, a total of 68 (30.8%) had abnormal ECG's at baseline. During these trials 17 (7.7%) patients had ECG abnormalities that were reported

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as adverse events. Apart from 1 patient (Trial 5 patient 0002/0081) who had a prolongation of the PR interval that was considered not clinically significant, none of these adverse events was considered by the investigator to be related to trial treatment. Electrocardiographic abnormalities are summarized in **Table 57**.

Table 57: Phase I abnormal ECG findings

Adverse event	Number (%) of patients a				All doses (n=270)
	<225 mg (n=51)	250 mg (n=75)	500 mg (n=72)	>525 mg (n=72)	
Arrhythmia	0(0.0)	0(0.0)	0(0.0)	1(1.4)	1(0.4)
Atrial Fibrillation	2(3.9)	0(0.0)	3(4.2)	0(0.0)	5(1.9)
AV block	0(0.0)	0(0.0)	1(1.4)	0(0.0)	1(0.4)
ECG abnormal	1(2.0)	1(1.3)	1(1.4)	3(4.2)	6(2.2)
Sinus bradycardia	0(0.0)	0(0)	2(2.8)	0(0.0)	2(0.7)
Tachycardia	2(3.9)	3(4.0)	0(0.0)	0(0.0)	5(1.9)
Ventricular extrasystoles	0(0.0)	3(4.0)	1(1.4)	0(0.0)	4(1.5)

a patients might have more than one ECG abnormality

Phase II monotherapy studies

In the Phase II studies patients had a screening and withdrawal ECG and, additionally in trial 16, an ECG at the end of month 4.

At trial entry, 153 (36%) patients had abnormal ECG results. Of these patients, 46 were from trial 16 and 107 were from trial 39. During the trials 10 patients (4 at 250 mg/day and 6 at 500 mg/day) had ECG abnormalities reported as adverse events. Three of these patients had abnormal ECGs at baseline. Five of the events (2 arrhythmias and 3 atrial fibrillations) were CTC Grade 3 and the others were CTC Grade 1 or 2. Only 1 of these adverse events was considered by the investigator to be related to trial treatment (non-serious, grade 3 atrial fibrillation) and 1 was reported as serious (unrelated, grade 3 atrial fibrillation). One of these 10 patients and an additional patient had a myocardial infarction and died within 30 days after trial treatment ended. Details of these 11 patients is as follows:

Trial 16

Patient 0804/0004 (250-mg/day group) had related, non-serious Grade 3 atrial fibrillation recorded after 87 days treatment, at the time of withdrawal due to disease progression. The adverse event resolved.

Patient 0207/0004 (250-mg/day group) had unrelated, serious Grade 3 atrial fibrillation recorded after 8 days treatment, when he withdrew due to disease progression. The adverse event resolved.

Patient 0501/0004 (500-mg/day group) had unrelated, non-serious Grade 3 arrhythmia and lung edema, Grade 2 atrial fibrillation and serious Grade 4 dyspnea recorded 13 days after

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entering the trial, but only having received treatment on Day 1 and then withdrawing with objective disease progression.

Trial 39

Patient 2008/0192 (500-mg/day group) had non-drug-related, CTC Grade 1 ectopic beats recorded after 8 days of treatment. The patient received 41 days of trial treatment. The adverse event was reported as ongoing.

Patient 2107/0035 (500-mg/day group) had non-drug-related, CTC Grade 3 irregular heart rhythm recorded 6 days after an acute myocardial infarction, which occurred on the same day the patient was withdrawn from the trial due to adverse events (drug-related diarrhea and non-drug-related myocardial infarction). The patient also had disseminated intravascular coagulation at the same time as the arrhythmia. The patient died 1 day after the onset of these events. The patient had a history of myocardial infarction and atrial fibrillation. The patient received 63 days of trial treatment.

Patient 2028/0105 (500-mg/day group) had non-drug-related, CTC Grade 3 atrial fibrillation recorded after 39 days of treatment. The adverse event resolved 3 days later. The patient received 45 days of trial treatment.

Patient 2107/0036 (500-mg/day group) had non-drug-related, CTC Grade 2 atrial fibrillation recorded after 6 days of treatment. The adverse event was reported as ongoing. The patient was withdrawn from the trial due to non-drug-related adverse events (congestive heart failure, hypoxia, and acute respiratory distress) after 7 days of treatment and died 7 days later of complications due to lung cancer.

Patient 2101/0155 (250-mg/day group) had non-drug-related, CTC Grade 1 T-wave inversion, Grade 1 axis deviation and Grade 1 left bundle branch block 2 days post treatment. Sinus tachycardia, sepsis, pneumonia, and dehydration were also reported at or near that time. The patient received 29 days of treatment and died due to metastatic NSCLC and sepsis 1 day after the ECG abnormalities were reported.

Patient 2101/0154 (250-mg/day group) had non-drug-related, CTC Grade 1 abnormal electrocardiogram recorded 1 day post treatment. The adverse event was reported as ongoing. The patient was withdrawn from the trial due to non-drug-related adverse events (respiratory failure and pneumonia) after 71 days of treatment.

Patient 2028/0107 (500-mg/day group) had non-drug-related, CTC Grade 1 premature ventricular contractions recorded after 163 days of treatment. The adverse event was ongoing. The patient received 195 days of treatment.

Patient 2107/0034 (250-mg/day group) had a history of myocardial infarction and had arrhythmia (CTC Grade 4) recorded as an adverse event, beginning prior to treatment. This patient died of a myocardial infarction 25 days after trial treatment ended. The patient received 111 days of trial treatment. The QTc interval at baseline was 420 msec; no follow-up ECG was performed.

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These events from the 2 Phase II monotherapy studies are summarized in **Table 58**.

Table 58: ECG abnormalities

Adverse event	Number (%) of patients	
	ZD1839 250 mg/day N=205	ZD1839 500 mg/day N=220
Arrhythmia	1(0.5)	3(1.4)
Atrial Fibrillation	2(1.0)	3(1.4)
Bundle branch block	3(1.5)	0(0.0)
Electrocardiogram abnormal	2(1.0)	0(0.0)
Myocardial infarct	1(0.5)	1(0.5)
Palpitation	1(0.5)	3(1.4)
Sinus bradycardia	0(0.0)	1(0.5)
Tachycardia	5(2.4)	7(3.2)
Ventricular extrasystoles	0(0.0)	1(0.5)

There were no clear trends observed in ECGs or PR intervals for patients during trial treatment and no apparent differences between the doses. In Trial 0039, corrected QT interval was recorded at trial entry and withdrawal. Forty-two patients had their withdrawal ECG within 24 hours of the last dose of ZD1839. For these patients, there was no evidence of any prolongation of QT interval over the course of the trial,

7.6 Adequacy of Safety Testing

Safety data from Phase I and Phase II studies of relatively short follow-up suggest that ZD1839 is generally well tolerated. Long duration safety data is not yet available. It was of interest to observe that the ophthalmologic toxicity noted in pre-clinical studies was not observed in study patients.

7.7 Safety Conclusions

A total of 960 subjects (714 cancer patients, and 246 healthy volunteers) were exposed to ZD1839 in the 20 completed monotherapy trials. A total of 420 subjects (297 cancer patients, and 123 healthy volunteers) were exposed to a dose of ZDI 839 between 225 and 300 mg/day, with a maximum duration of dosing of 506 days. A total of 348 subjects (292 patients and 56 healthy volunteers) were exposed to a dose of ZDI 839 between 400 and 525 mg/day, with a maximum duration of dosing of 404 days.

Patients receiving ZD1839 250 mg/day (or similar doses) in the multiple-dose Phase I and II trials frequently experienced drug-related gastrointestinal disturbances (mainly diarrhea, sometimes associated with dehydration) and skin reactions (rash, acne, dry skin, and pruritus). The majority of drug-related adverse events were mild (CTC Grade 1) and non-cumulative, and rarely led to withdrawal of ZD1839 therapy, with only 2 CTC Grade 3 diarrheas, and 3 CTC Grade 3 skin events reported at the 250-mg/day dose in the Phase II trials.

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No additional safety concerns were raised for subpopulations of men or women, the elderly, ethnic groups, patients with renal impairment, or patients with mild to moderate hepatic impairment. Evaluation of the safety data does not indicate the need for any additional safety monitoring. Few specific drug-drug interactions have been identified that could impact on the safety of ZD1839.

In patients receiving ZD1839 therapy, there have been infrequent reports of reversible corneal erosion, sometimes in association with aberrant eyelash growth. However, no evidence of any consistent or drug-related ophthalmologic toxicity was observed in the Phase II trials. Consequently, no recommendations or precautions relating to eye events are considered necessary beyond patients being aware that they should seek medical advice should they develop any eye symptoms.

Data from non-clinical, in vitro studies indicate that ZD1839 has the potential to inhibit the cardiac potential repolarization process eg, QTc interval. The clinical relevance of these findings is unknown. No clear trends were observed in ECGs or PR intervals in patients participating in the Phase II trials.

A small number of significant, asymptomatic increases in liver transaminases have been observed at the 250-mg/day dose.

There was 1 report each of toxic epidermal necrolysis and erythema multiforme.

Co-administration of ZD1839 250 mg with itraconazole, a CYP3A4 inhibitor, resulted in an 80% increase in the mean AUC of ZD1839 in healthy volunteers. This increase maybe clinically relevant to the safety of ZD1839 when used concomitantly with drugs that inhibit CYP3A4, since drug-related adverse events are related to dose and exposure.

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on ZD1839 therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time and INR.

In conclusion, the adverse event data reported in the Phase II and I trials conducted with ZD1839 indicate that this drug has a favorable safety profile for the intended patient population. Overall, the 250-mg/day dose was better tolerated than the 500-mg/day dose.

7 Dosing, Regimen and Administration Issues

In the Phase I program, anti-tumor activity with tumor regression occurred in patients at ZD1839 doses from 150 mg/day to 800 mg/day. Pharmacokinetic data in patients showed up to a 8-fold interpatient exposure variability at a given dose level. Since the lowest dose at which responses were first seen was 150 mg, a minimum dose of 250 mg was chosen to minimize the chance that patients would have exposure that was below a theoretical threshold. Since median steady state plasma concentrations of the 225- and 525-mg dose levels did not overlap by more than approximately 30%, there appeared to be the potential for discrimination between doses. Upper dose levels were selected on the basis of dose-limiting toxicity and tolerability. Therefore, the higher dose of 500 mg was chosen as

a dose at which ZD1839 can be taken by the patient daily with small likelihood of therapy interruption or dose reduction.

In both the pivotal Trial 39 and supportive Trial 16, there were no significant differences between the 250 mg/day and 500 mg/day dose groups in regards to tumor response rates and disease-related symptom improvement rates. FACT-L and TOI improvement rates were higher in the 250-mg/day group than the 500-mg/day group in both trials. This may in part reflect the lower toxicity seen at the 250-mg dose. Overall, the 250-mg dose is as effective as the 500-mg dose.

9 Use in Special Populations

9.1 Tumor response by subgroups sex, age, and ethnicity

More women experienced tumor responses at either the 250-mg/day and 500-mg/day doses (23.8%; 95% CI: 12.1%, 39.5%] and 15.7%; 95% CI: 7.0%, 28.6%, respectively) than men (3.3%; 95% CI: 0.4%, 11.5% and 3.2%; 95% CI: 0.4%, 11.0%, 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. Similar tumor response rates were seen between the 2 dose groups for white patients; however, there were not enough non-white patients to draw any conclusions between patients of different ethnic origins.

9.2 Symptom improvement by the subgroups sex, age, and ethnicity

The symptom improvement rates, as assessed by the sponsor, were higher in female patients in both dose groups: 50.0% (95% CI: 34.2%, 65.8%; 250-mg/day group) and 49.0% (95% CI: 34.8%, 63.4%; 500-mg/day group) than male patients (38.3%, 95% CI: 26.1%, 51.8%; 250-mg/day group and 23.8%, 95% CI: 14.0%, 36.2%, 500-mg/day group). No discernible pattern was observed for the sponsor's analysis of disease-related symptom improvement rates by age or ethnicity in either dose group.

9.3 Adverse Events In Special Populations-Studies - Phase II trials 39 and 16

9.3.1 Gender

Table 59 shows the incidence of 6 of the most common adverse events in the Phase II trials presented by gender. The incidence of diarrhea was higher in females than males for both doses.

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Table 59: Common adverse events by gender (Trials 39 and 16)

Adverse event	Number (%) of patients			
	250 mg dose		500 mg dose	
	Female (n=67)	Male (n=138)	Female (n=87)	Male (n=133)
Diarrhea	41(61.2)	67(48.6)	67(77.0)	89(66.9)
Rash	32(47.8)	66(47.8)	57(65.5)	80(60.2)
Asthenia	18(26.9)	37(26.8)	22(25.3)	42(31.6)
Dyspnea	13(19.4)	32(23.2)	14(16.1)	27(20.3)
Nausea	20(29.9)	32(23.2)	26(29.9)	42(31.6)
Acne	18(26.9)	21 (15.2)	21 (24.1)	34(25.6)

9.3.2 Ethnic origin

Data for patients other than those of White or Asian origin, is insufficient for analysis.

9.3.3 Age

Table 60 shows adverse events by age categories (<45 years; 45 to 64 years; 65 to 74 years; ≥75 years. As no trials have been conducted in subjects <18 years of age, the safety of ZDI 839 cannot be assessed in pediatric patients. For all age groups there is more toxicity for the 500 mg/day dose than for the 250 mg/day dose. Within each dose, however, there does not seem to be significantly different toxicity by age. The small numbers of patients >75 years of age makes it difficult to draw conclusions on this group.

Table 60: Common adverse events presented by age (pooled data from Trials 39 and 16)

Adverse event	Number (%) of patients							
	250 mg dose				500 mg dose			
	<45 years (n=16)	45 to 64 years (n=116)	65 to 74 years (n=62)	≥75 years (n=11)	<45 years (n=21)	45 to 64 years (n=122)	65 to 74 years (n=67)	≥75 years (n=10)
Diarrhea	8(50.0)	59(50.9)	34(54.8)	7(63.6)	13 (61.9)	88(72.1)	49(73.1)	6(60.0)
Rash	9(56.3)	51 (44.0)	30(48.4)	8(72.7)	13 (61.9)	80(65.6)	38(56.7)	6(60.0)
Asthenia	3 (18.8)	31 (26.7)	18(29.0)	3(27.3)	2(9.5)	38(31.1)	19(28.4)	5(50.0)
Dyspnea	4(25.0)	28(24.1)	11 (17.7)	2(18.2)	2(9.5)	24(19.7)	14(20.9)	1 (10.0)
Nausea	3 (18.8)	26(22.4)	20(32.3)	3 (27.3)	9(42.9)	38(31.1)	17(25.4)	4(40.0)
Acne	5 (31.3)	23 (19.8)	11 (17.7)	0(0.0)	1(4.8)	29(23.8)	22(32.8)	3(30.0)

9.3.4 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.

9.3.5 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.

9.3.6 Safety of ZD1839 when given in combination with other drugs

ZD1839 showed no enzyme induction effects in animal studies.

ZD 1839 inhibited CYP2D6 by <50% in vitro, and the magnitude of the interaction with metoprolol, a CYP2D6 substrate was tested in Trial 0038. In this trial, there was no evidence of a clinically significant change to metoprolol exposure when co-administered with ZD1839 500 mg/day.

CYP3A4 inhibitors and inducers

ZD1 839 is metabolised by CYP3A4 in vitro and may be affected by co-administration of drugs which are inhibitors or inducers of CYP3A4 in man. The magnitude of such interactions has been assessed clinically using itraconazole, a selective inhibitor of CYP3A4 (Trials 0027 and 0051), and rifampicin, a potent but relatively non-specific inducer of CYP3A4 (Trial 0030). As anticipated, co-administration of itraconazole or rifampicin with ZD1839 increased and decreased exposure to ZD1839, respectively.

A review of adverse events data according to whether patients received concomitant CYP3A4 inhibitors or inducers, respectively, shows:

- The profile of adverse events was generally similar for patients receiving CYP3A4 inhibitors or inducers to those not receiving such drugs.
- The concomitant use of either CYP3A4 inhibitors or inducers appeared to increase the incidence of certain adverse events eg, nausea and vomiting. These effects may have been due to the drugs themselves rather than due to a drug interaction with ZD 183 9.

Drugs which lower gastric acidity

The 250 mg tablet formulation of ZD1839 shows a significant reduction in dissolution between pH 4 and 5. Consequently, it is possible that an increase in gastric pH could reduce the bioavailability of oral Z131839. Trial 0036 was conducted to assess the effect of increased gastric pH on the relative bioavailability of a 250 mg oral dose of ZD1839 in healthy male volunteers. The increase in gastric pH achieved in these volunteers, and the duration over which elevated gastric pH was maintained, were considered to be higher and for longer than might be achieved with standard antacid treatment. However, systemic elevation of gastric pH resulted in a reduction in exposure to ZD1839, and as such, did not present any concern regarding the safety of ZD1839.

Vitamin K antagonists

A total of 37 bleeding events in 31 patients taking warfarin concomitantly with ZD1839 were identified from across the ZD1839 clinical trial program. Based on these findings it was concluded that patients taking warfarin while on ZD1839 therapy should be monitored regularly for changes in PT (prothrombin time) or INR (International Normalized Ratio).

9.3.7 Safety Of ZD1839 In Pregnancy And Lactating Women

The safety of ZD1839 in pregnant or breast-feeding women has not been established in clinical trials.

It is not known whether ZD1839 is excreted in human milk. Following oral administration of carbon-14 labeled ZD1839 to rats 14 days postpartum, concentrations of radioactivity in milk were higher than in blood. Levels of ZD1839 and its metabolites were 11 to 19-fold higher in milk than in blood, after oral exposure of lactating rats to a dose of 5 mg/kg.

10 Conclusions and Recommendations

10.1 Efficacy

See pages 67-69.

10.2 Safety

See pages 103-108

10.3 Recommendation

The Medical Officer defers making a final recommendation on approval until after the ODAC discussion and recommendation. Factors that will have to be considered by ODAC include 1) the 11 percent response rate observed in Trial 39 patients and in Caucasian patients in Trial 16; 2) the difficulty in interpreting quality of life/symptom relief data in phase II trials; 3) the uncertain effect of concomitant medication on symptom and quality of life improvement; 4) the characteristics of the responding patient population, (largely comprised of individuals with slow growing, less biologically aggressive tumors) and 5) the results of the two recently completed phase III first-line NSCLC ZD1839 trials that unequivocally failed to demonstrate clinical benefit.