AstraZeneca

ODAC Briefing Document

Drug Substance IRESSA (gefitinib)

IRESSA® (ZD1839, gefitinib)* TABLETS

FDA Advisory Committee Meeting Briefing Document NDA 21-399 for the use of IRESSA for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received platinum-based chemotherapy

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*IRESSA is used within this document to indicate both the formulated drug product as well as the unformulated drug substance, ZD1839.

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ABBREVIATIONS

Abbreviations	Term
4-MSU	Four-month Safety Update
ALT/SGPT.	Alanine aminotransferase/serum glutamic pyruvic transaminase
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase.
AUC	area under the concentration-time curve
BSC	best supportive care
CI	confidence interval
CR	complete response
CTC	common toxicity criteria
DLT	dose limiting toxicity
EGFR	epidermal growth factor receptor
FACT-L	Functional Assessment of Cancer Therapy - Lung
INR	International Normalized Ratio
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety Information
ITT	intent-to-treat
LCS	Lung Cancer Subscale
NDA	new drug application
NSCLC	non-small cell lung cancer
QOL	quality of life
PD	progressive disease
PP	per protocol
PR	partial response
PRNM	partial response in non-measurable disease
REC	Response Evaluation Committee
RTK	receptor tyrosine kinase
SAE	serious adverse event
SWOG	Southwest Oncology Group
SD	stable disease
TK	tyrosine kinase
UICC	Union Internationale Contre le Cancer

ABBREVIATIONS (continued)

Abbreviations	Term
WHO	World Health Organization

SUMMARY

Background

Patients with advanced NSCLC have a poor prognosis with 1 to 5% five-year survival rates. Use of platinum-based chemotherapy associated with improved 1-year survival rates and use of docetaxel at subsequent recurrence is now resulting in greater numbers of surviving patients in need of further therapy. After prior platinum and docetaxel therapy, there is no proven beneficial therapy and median survival is 4 to 6 months. Patients experience increasing severity and frequency of disease-related symptoms, especially pulmonary symptoms, which are accompanied by inevitable disease progression and cancer-related death.

IRESSA is an oral, novel, molecularly targeted agent that has provided evidence for clinical benefit in this area of unmet need for palliation. Durable objective radiographic responses were accompanied by sustained improvement in disease-related symptoms and quality of life. These findings were demonstrated in 2 randomized clinical trials conducted concurrently in US and outside the US.

Clinical trial design of the Phase II program

Efficacy and safety data were obtained from 2 multicenter, randomized, double-blind, clinical trials: pivotal Trial 0039 and supportive Trial 0016. Differences in the design of these trials were primarily twofold. First, the requirement for prior chemotherapy regimens differed between the 2 trials. Trial 0039 required at least 2 prior regimens, including both platinum and docetaxel. Patients must have discontinued their most recent chemotherapy due to disease progression or unacceptable toxicity (within 90 days of their last dose). Trial 0016 required no more than 2 prior regimens, one of which was platinum-based. Second, Trial 0016 had the requirement to enter at least 100 patients from Japan. Trial 0039 randomized 216 patients and Trial 0016 randomized 209 patients. In both trials, patients with locally advanced or metastatic NSCLC after platinum therapy were randomized to receive daily oral doses of 250 mg or 500 mg IRESSA. Efficacy was determined by 2 co-primary endpoints: as a) confirmed objective tumor response, and b) clinically significant improvement in disease-related symptoms for at least 1 month.

All patients in Trial 0039 were required to have disease-related symptoms as assessed by a validated scoring method. In contrast, Trial 0016 patients did not have to be symptomatic at trial entry.

Benefits of IRESSA®[1] (ZD1839, gefitinib) therapy patients previously treated for NSCLC

In both trials, there were no major demographic, disease, or prior therapy differences in patients randomized to either dose. Overall, efficacy and safety findings were consistent between the 2 trials, and the 250-mg dose was as effective as, and better tolerated than, the 500-mg/day dose. Clinically significant objective radiographic and symptom improvement

[1] IRESSA is a trademark of the AstraZeneca group of companies.

responses were seen at both 250-mg and 500-mg dose levels in both trials. A total of 12 (11.8%; 95% CI: 6.2%, 19.7%) patients in Trial 0039 showed partial responses in the 250-mg/day group, which was significantly greater than the prospectively-defined lower limit of 5% (p=0.005). Ten (8.8%; 95% CI: 4.3%, 15.5%) patients showed partial responses in the 500-mg/day group. In Trial 0016, a total of 19 (18.4%; 95% CI: 11.5%, 27.3%) patients showed partial responses in the 250-mg/day group while 20 (19.0%; 95% CI: 12.1%, 27.9%) patients showed tumor responses in the 500-mg/day group.

Prospectively defined, clinically significant disease-related symptom improvement for at least 1 month was observed in approximately 40% of all patients in Trial 0039 for both dosese. Similar results were achieved among the symptomatic patients at baseline in Trial 0016. Symptom improvement was typically seen by Week 4. Onset of symptom improvement generally preceded objective evidence of radiographic response or disease stabilization and occurred rapidly within 8 to 10 days. At entry in both trials, over 90% of the symptomatic patients had 1 or more pulmonary symptoms with shortness of breath, coughing, and difficulty breathing being most frequent and severe. In both trials, approximately one-third of symptomatic patients experienced improvement in each of the four pulmonary symptoms with approximately one-quarter of patients reporting some degree of improvement in 1 to 2 pulmonary symptoms and one-third reporting some degree of improvement in 3 to 4 pulmonary symptoms. Reflecting the degree of tumor reduction or control, symptom relief, and low toxicity observed, up to one-third of patients experienced prospectively defined, clinically significant improvement in their Quality of Life in both dose groups across both trials.

Objective tumor response and stable disease were associated with disease-related symptom improvement in both trials. In Trial 0039, 21 out of the 22 (95.5%) patients with objective response and 71% of patients with stable disease had disease-related symptom improvement. In contrast, only 16.8% of patients with a best response of disease progression had disease-related symptom improvement. In Trial 0016, approximately 78% of symptomatic patients with objective tumor response and more than half of patients with stable disease had symptom improvement. Of the patients with progressive disease, 13.2% had improvement in disease-related symptoms. Across both trials and dose groups, better survival was consistently associated with objective response, and disease-related symptom improvement than those without these outcomes.

Drug-related gastrointestinal disturbances (mainly diarrhea) and skin reactions (rash, acne, dry skin, and pruritus) were frequent although the majority were mild (CTC Grade 1). These adverse events were non-cumulative and led to withdrawal or temporary therapy cessation infrequently (≤10%) at the higher dose and rarely (≤1%) at the lower dose. Overall, a low frequency of clinically significant side effects occurred especially at the 250-mg dose.

The 250-mg/day dose was as effective as, and better tolerated than the 500-mg/day dose, and therefore is the recommended dose.

IRESSA provides an excellent palliative benefit for symptomatic patients with previously treated, advanced NSCLC. The recommended daily dose of 250 mg with a favorable safety

profile and good tolerability offers an important therapeutic addition for patients with locally advanced or metastatic NSCLC who have previously received platinum-based chemotherapy.

1 INTRODUCTION

1.1 Indication

This document provides a summary of the clinical program for IRESSA® (IRESSA, ZD1839, gefitinib), background information, descriptions of the approach and rationale for its clinical development, and key efficacy and safety results and conclusions from clinical trials. A New Drug Application (NDA 21-399) was submitted to the FDA for the use of IRESSA for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received platinum-based chemotherapy.

1.2 Order of presentation and conventions

Section 2 of this document presents general information about the development of the IRESSA clinical program and the data included in the NDA. Section 3 presents a summary of clinical pharmacology data, Section 4 presents a summary of the efficacy results from the Phase II trials that contributed to the evaluation of IRESSA as an effective treatment for advanced NSCLC, and Section 5 presents a summary of the safety results from the clinical trial program followed by conclusions from the 4-month Safety Update Report. Section 6 presents overall conclusions about the clinical program. Appendix A presents prescribing implications. Data cutoff dates for assessments and analyses will be defined in sections where appropriate.

2 BACKGROUND

2.1 Pharmacologic class

Among the first to be developed in its class, IRESSA is an orally active, selective inhibitor of the epidermal growth factor receptor-tyrosine kinase (EGFR-TK) with a biologically based mode of action distinct from cytotoxic chemotherapy. IRESSA is an anilinoquinazoline with a molecular weight of 446.9.

2.2 Clinical background and treatment of advanced NSCLC

Lung cancer is the leading cause of cancer-related deaths in both men and women in the United States (Ferlay et al 2001). In women, the incidence is steadily and dramatically rising. Previously treated patients with advanced NSCLC have a median survival of 4.5 months (Shepherd et al 2001). With advances in the treatment of newly diagnosed, advanced NSCLC, survival in patients able to receive chemotherapy has modestly improved over the past 2 decades (Breathnach et al 2001). With newer platinum-based regimens, the response rate is approximately 20%, while the median survival has increased to approximately 8 months and the 1-year survival rate has increased from 10% to 35% (Ginsberg et al 1997, Schiller 2001). With recurrence or progression, docetaxel has improved 1-year survival rates from approximately 19% to almost 30%. As a result of platinum-based therapy and docetaxel, and the increasing usage of chemotherapy for advanced NSCLC, larger numbers of patients are

surviving longer although the 5-year survival rate of 1 to 5% remains unchanged from that seen decades ago with historic untreated advanced NSCLC patients (Ries et al 2001).

Two randomized trials have been conducted in NSCLC patients who have previously received platinum-based chemotherapy where limited improvements were observed (Shepherd et al 2000). In 1 trial, patients were randomized to docetaxel at 100 mg/m^2 but the dose was reduced halfway through the trial to 75mg/m^2 due to 5 possibly treatment-related deaths within first 30 days. With docetaxel, the overall response rate was 5.8%. Among the responding patients, the time interval from the most recent chemotherapy varied from 1 to 21 months; none of the 25% patients with a performance status of 2 had a response. Among docetaxel-treated patients, 50% had disease control with either response or stable disease. Median survival and 1-year survival was significantly improved with docetaxel compared to patients in the best supportive care (BSC) arm (7.0 months vs 4.6 months, and 29% vs 19%, respectively). When docetaxel was given at the lower dose of 75mg/m^2 and preceded for 5 days by dexamethasone pre-medication, hematologic toxicity was common, Grade 3 or 4 neutropenia occurred in 67% of patients and anemia in 5.5% of patients. Non-hematologic toxicity was common and included Grade 1 or 2 fever in over one-half, diarrhea, infection, nausea, stomatitis and/or pulmonary symptoms in approximately one-third, neurosensory and/or vomiting in one-quarter as well as fluid retention in 12%. One quarter of patients received radiotherapy while on study. Patients in the BSC group had adverse events, either directly or indirectly related to disease, including Grade 3 or 4 pulmonary events in approximately 33% of patients, severe asthenia and/or documented infection in about 25% of patients, and mild to moderate fluid retention and/or Grade 3 or 4 anemia in about 10% of patients.

The second trial randomized patients who progressed during or after 1 or more platinum regimens. Patients were randomized into 1 of 3 arms: docetaxel 100 mg/m^2, docetaxel 75mg/m^2, or other single agent chemotherapy (vinorelbine or ifosfamide). Response rates were 10.8%, 6.7%, and 0.8% for docetaxel 100 mg/m^2, 75 mg/m^2 and comparison arms, respectively. The median time to progression and median survivals for the 3 arms was almost identical (7.9 to 8.5 weeks and 5.5 to 5.7months, respectively) as was overall survival (primary efficacy endpoint). The estimated 1-year 32% survival was better for the 75 mg/m^2 docetaxel group than1 year 19% survival with vinorelbine/ifosfamide (chi square test, p=0.025) and 21% 1-year survival of docetaxel 100-mg/m^2 group. Hematologic and non-hematologic toxicity with docetaxel was similar to that previously reported with the exception of febrile neutropenia due to use of filgastrim. Types of Grade 3 or 4 type toxicity reported with vinorelbine/ifosfamide were similar with the major exception of a 31% incidence of neutropenia. Overall, 11% of patients discontinued therapy due to treatment-related adverse events.

Currently, there are no proven effective therapies for patients following prior platinum and docetaxel therapies. These patients can either receive no further anti-cancer therapy of any type, be included in various Phase I trials if they can meet eligibility requirements and wish to participate, or receive commercially available chemotherapy agents.

In the absence of effective chemotherapy, disease will progress with the outcomes similar to those newly diagnosed, untreated patients, and patients with recurrent disease, or ineffectively treated patients. Indirect support for this assumption is seen in the study results described above and in a recent retrospective chart-based review of 43 patients with advanced recurrent NSCLC who had received two prior chemotherapy regimens, which included platinum and docetaxel given simultaneously or concurrently. A variety of chemotherapy agents and/or regimens, most frequently with gemcitabine, vinorelbine, or additional platinum, found a response rate of 2% and 0% for third and fourth therapy attempts, respectively, and median survival was 4 months from the time of the third treatment (Massarelli et al 2002). Shepherd recently updated survival of patients who had received docetaxel as third- or more-line treatment and reported a subsequent median survival of 4 months, which was equal to that of similar patients who received BSC (Frances Shepherd personal communication).

Quality of life (QOL) is a broad assessment by the patient of the combined impact of disease and treatment. Improvement in disease-related symptoms is the component that is most directly the result of effective therapy intervention, and is an outcome of primary importance in the palliative setting of NSCLC (American Society of Clinical Oncology 1997). Advanced NSCLC is a disease of symptoms by virtue of its anatomic primary and metastatic location in the lung. At diagnosis, 80% to 90% of patients with advanced NSCLC have1 or more disease-related symptoms including pulmonary-specific symptoms of shortness of breath, cough, difficulty breathing, and chest tightness as well as non-specific symptoms of advanced cancer (Cella et al 1995, Cella et al 2002). In 1 series of 673 patients with advanced NSCLC at diagnosis, 36% of patients had 5 or more symptoms, 45% had 3 to 4 symptoms, and 17% had 1 to 2 symptoms. Randomized trials comparing chemotherapy with best supportive care in newly diagnosed patients with advanced disease have shown that disease-related symptoms and QOL to improve with chemotherapy and usually deteriorate with best support care (Cullen et al 1999, Gridelli 2001, Tummarello et al 1995, Thatcher et al 1995). This improvement occurs despite the well-known significant, common, and occasionally life-threatening side effects of chemotherapy, many of which were detailed above. With disease recurrence or progression, increasing tumor burden results in recurrence or worsening of disease-related symptoms. With best supportive care in the recurrent disease setting, improvements in QOL and disease-related symptoms occur in either a minority or none of patients (Shepherd et al 2001).

Novel, biologically based agents with clinically significant anti-tumor activity accompanied by significant disease-related symptom improvement in this patient population would fulfill an unmet need. Due to the combination of advanced disease, residual clinical or subclinical effects of prior chemotherapy (and radiation therapy in many patients), and co-morbidity, the safety profile must be both modest and not overlap with prior therapy sequelae.

2.3 Rationale for the development of IRESSA

The epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy as inhibition of receptor activation blocks signal transduction pathways implicated in proliferation and survival of cancer cells (Negoro et al 2001, Ranson et al 2002). EGFR is expressed in a variety of tumors, including NSCLC (Rusch et al 1993, Salomon et al 1995).

In several retrospective studies, high levels of EGFR expression have been associated with a poor prognosis in NSCLC patients (Fujino et al 1996, Pavelic et al 1993, Volm et al 1998). EGFR-targeted cancer therapies are currently being developed; strategies include inhibition of the intracellular tyrosine kinase (TK) domain of the receptor by small molecules such as IRESSA (Lawrence and Niu 1998).

2.4 Preclinical data

A number of tyrosine kinases exist as integral components of transmembrane receptor molecules and are classified as receptor tyrosine kinases (RTKs). There are several members of this family of RTKs, Class 1 of which includes receptors of the erbB family, eg, EGFR, erbB2, erbB3, and erbB4. Activation causes EGFR itself and a number of cellular substrates to become phosphorylated. These phosphorylation reactions are a major component of growth factor-induced mitogenic proliferation, the upregulation of the expression of vascular endothelial growth factor (Radinski 2000), the prevention of apoptosis (Moyer et al 2000, Bruns et al 2000) and the promotion of mobility, adhesion, and invasion (O-charoenrat et al 2000) in tumor cells (Woodburn 1999). Effective inhibition of the EGFR TK results in the reversal of these critical aspects of tumor biology.

2.4.1 Preclinical pharmacology

Pharmacology studies provided the following key additional relevant findings about IRESSA:

- Selective, submicromolar inhibition of isolated EGFR tyrosine kinase.
- IRESSA inhibited EGF-stimulated EGFR autophosphorylation in tumor cells in a sustained dose-dependent and complete manner.
- IRESSA selectively inhibited EGF-stimulated tumor cell growth in vitro.
- IRESSA inhibited the growth of a wide range of human NSCLC and other tumor xenografts in nude mice in a dose-dependent and reversible manner.
- In vivo anti-tumor activity is associated with dose-dependent, reversible inhibition of the downstream signal transduction biomarker, c-*fos*.
- The level of EGFR expression generally does not correlate with the degree of tumor xenograft sensitivity to IRESSA.
- IRESSA enhanced the efficacy of cytotoxic-, radiation- and hormone antagonist-treatment of tumor cells in vitro, and the anti-tumor efficacy of cytotoxic drug treatment in tumor xenografts.
- Anti-tumor efficacy was achieved in nude mice tumor xenografts with once daily, oral dosing; interruption of dosing resulted in resumption of tumor growth at a rate similar to untreated controls.

2.4.2 Preclinical safety evaluation

A complete series of animal toxicology studies were conducted, and a summary of the key results of these studies is presented below:

- There was no evidence of genotoxicity.
- The principal pathological changes were observed in the ovaries (atrophy), eyes (reversible corneal translucencies which progressed in dogs to corneal opacities on extended dosing at high doses), kidneys (papillary necrosis), skin (acute dermatitis/folliculitis) and liver (transient transaminase elevation, with hepatocellular necrosis being observed in the 6-month rat study at the highest dose of 200 mg/kg). These observations are generally consistent with the pharmacological activity of IRESSA (inhibition of EGFR TK).
- Data in isolated dog Purkinje fibers and in an in vitro cloned potassium channel assay indicated that IRESSA has a modest potential to cause repolarization abnormality and hence, potentially prolong QT intervals. In addition, occasional reversible prolonged P-R intervals were observed in dogs.

3 CLINICAL PHARMACOLOGY AND PHASE I RESULTS

3.1 Clinical pharmacology results

3.1.1 Overview

This section summarizes the Phase I clinical pharmacology trials conducted to determine the bioavailability and pharmacokinetics of IRESSA. Pharmacokinetic data have also been obtained from the Phase I trials conducted in patients with solid tumors (Trials 0005, V-15-11, 0011, and 0012) and from the Phase II monotherapy trials (Trials 0039 and 0016) conducted in patients with advanced NSCLC.

The pharmacokinetic characteristics of IRESSA have been characterized following single intravenous (iv) administration and following both single and multiple oral dosing.

The clinical pharmacology trials conducted in healthy volunteers involved male subjects only due to evidence obtained from animal studies of slight fetal toxicity and reduced female fertility. Trials involving cancer patients recruited both male and female subjects, and results from those trials have shown no evidence of any differences in the pharmacokinetics of IRESSA based on gender, thus validating the use of male volunteers.

3.1.2 Pharmacokinetic and metabolism data

3.1.2.1 Single-dose pharmacokinetics of IRESSA

Following single-dose intravenous administration to both healthy volunteers and cancer patients, IRESSA was extensively distributed out of the blood (mean volume of distribution at steady state was approximately 1600 and 1400 L, respectively) and rapidly cleared. Mean

plasma clearance in healthy subjects was approximately double that in cancer patients (840 and 514 ml/min, respectively) and the mean terminal half-lives were 34 and 48 hours respectively.

Following single oral administration, absorption of IRESSA was moderately slow, with maximum plasma concentrations typically observed between 3 and 7 hours post-dose. Beyond the peak, plasma concentrations typically declined biphasically with mean terminal half-lives of 30.5 hours in healthy volunteers and 41 hours in patients. The absolute bioavailability of the 250-mg oral dose was approximately 60%. Exposure (area under the concentration-time curve [AUC]) at a given dose level in both groups of individuals was variable (up to a 20-fold range in healthy volunteers and up to an 8-fold range in cancer patients) and increased with increasing dose (dose proportionally in healthy volunteers over the dose range 50 to 250 mg). Exposure was not altered to any clinically significant extent by food (35% increase in relative bioavailability in fed volunteers) but was reduced (47% reduction in relative bioavailability) under conditions of sustained elevated gastric pH.

3.1.2.2 Multiple-dose pharmacokinetics of IRESSA

Consistent with the single-dose terminal half-life data, daily oral dosing of IRESSA resulted in accumulation (typically 2 to 8-fold in cancer patients) with steady state exposures achieved within 7 to 10 days of the start of treatment. Multiple dose plasma concentration-time profiles were fairly flat with concentrations maintained for each individual within a 2- to 3-fold range across the 24-hour dosing interval. Steady state exposure to IRESSA (AUC_{0-24}) was not always well predicted from single-dose data, with the ratio of steady state AUC_{0-24} to single-dose AUC in healthy volunteers ranging from 0.55 to 1.84 and from 0.58 to 2.38 in cancer patients. This may have been a consequence of day-to-day variation in the absorption/bioavailability of IRESSA.

Population data from the 2 Phase II studies conducted in patients with advanced non-small cell lung cancer showed that the mean predicted steady state trough concentration following a 250-mg oral dose was 261 ng/ml (95% CI: 88.0 to 774 ng/ml) with interpatient variability of 56% and intrapatient variability of between 21% and 30%.

3.1.2.3 Population pharmacokinetics

The objectives and results of the population pharmacokinetic analysis for the pooled data from the Phase II trials (Trials 0039 and 0016) have been reported in a stand-alone report. The conclusions from this investigation were:

- There was approximate proportionality between the 250- and 500-mg doses with regard to the mean population-predicted trough concentration.

- No clinically relevant demographic/pathophysiological covariates (age, race, gender, height, hepatic function, human serum albumin concentrations, α-1 acid glycoprotein concentration, total protein concentration, body mass index, body weight, or creatinine clearance) were identified

- There was no correlation between clinical efficacy (best overall tumor response or best overall disease-related symptom response) and the predicted steady-state trough concentrations.

- A correlation was identified between predicted steady state trough concentrations and the incidence of adverse events of acne/skin rash and diarrhea.

- There was no correlation between predicted steady state trough concentration and the incidence of nausea and/or vomiting or with increased levels of liver enzymes (alanine aminotransferase [AST] and aspartate aminotransferase [ALT]).

3.1.2.4 Plasma protein binding

Binding of IRESSA to human plasma proteins was 91%, was independent of IRESSA concentration, and showed no evidence of any gender difference. IRESSA was shown to bind to both human serum albumin and human α-1 acid glycoprotein with binding to the latter being dependent on the concentration of α-1 acid glycoprotein present. In the presence of physiologically relevant concentrations of human serum albumin (40 mg/ml) and high α-1 acid glycoprotein concentrations representative of those which can be observed in cancer patients, IRESSA binding increased from 87% to 91%, corresponding to a 30% decrease in free IRESSA concentrations. Although this reduction in the proportion of unbound IRESSA could theoretically have an impact on the clearance and/or volume of distribution of IRESSA, no relationship between steady state trough concentration and circulating concentration of α-1 acid glycoprotein was apparent in the data obtained from the clinical trials.

3.1.2.5 Metabolism

The metabolism of IRESSA is complex. At least 3 sites of biotransformation have been identified which result in the production of 5 identified circulating metabolites,1 of which is present in the plasma at concentrations similar to those of parent compound. None of the identified metabolites is thought to contribute significantly to the overall pharmacological activity of IRESSA.

The major route of elimination of radiolabelled IRESSA (Trial 0003) was via the feces (with approximately 86% of the radioactive dose recovered over 10 days), as parent compound plus metabolites. The large proportion of radioactivity eliminated in the feces was attributed to biliary excretion as opposed to incomplete absorption. Less than 4% of the radiolabelled dose was recovered in the urine.

3.1.2.6 Drug interactions with IRESSA

3.1.2.6.1 Drugs that inhibit or induce CYP3A4

In vitro data has shown that CYP3A4 is involved in the metabolism of IRESSA.

In a healthy volunteer drug interaction study, co-administration of rifampicin (a potent CYP3A4 inducer) with a 500-mg dose of IRESSA resulted in an 83% reduction in mean IRESSA AUC. Thus, co-medication with other CYP3A4 inducers (eg, phenytoin,

carbamazepine, barbiturates, St John's Wort) may reduce exposure to IRESSA and potentially reduce efficacy.

In a further healthy volunteer drug interaction study, co-administration of itraconazole (a CYP3A4 inhibitor) with 250-mg and 500-mg doses of IRESSA resulted in increases of approximately 80%, and 60%, respectively in mean IRESSA AUC; the clinical relevance of this observation needs to be considered in conjunction with safety data from patients receiving multiple doses, which demonstrate that the incidence of adverse events is related to both dose and exposure.

3.1.2.6.2 IRESSA inhibition of drug metabolism

Since in vitro studies indicated that IRESSA might have the potential to inhibit CYP2D6, the clinical relevance of this finding was evaluated in a trial conducted in cancer patients. Results from this trial demonstrated a small, but clinically insignificant, increase in exposure to the CYP2D6 substrate metoprolol when dosed in the presence of steady state IRESSA exposure (500-mg dose).

3.2 Phase I clinical program

Four Phase I/IIa trials (Phase I: Trials 0005 and V-15-11; Phase I/IIa: Trials 0011 and 0012) assessed in 252 patients the tolerability and pharmacokinetics of escalating doses from 50 mg to 1000 mg of IRESSA in pretreated patients with solid tumors including 100 patients with heavily pretreated advanced NSCLC. In the first 2 Phase I trials (Trials 0005 and V-15-11), exposure to IRESSA was limited to once-daily oral dosing for 14 consecutive days followed by 14 days without IRESSA to ensure no irreversible changes were seen. Patients benefiting from IRESSA were then allowed to receive additional therapy at the same dose and schedule. The resultant safety profile in the first 2 Phase I trials allowed further evaluation of escalating doses given in the continuous daily dosing schedule in the subsequent 2 Phase I trials which was found to be optimal for tumor growth inhibition in preclinical studies (Trials 11 and 12).

3.2.1 Safety and anti-tumor activity

Most common drug-related, dose-related adverse events were Grade 1-2 skin rash and diarrhea. Dose-limiting diarrheal toxicity (DLT) occurred at the 800- or 1000-mg continuous daily dose level. Confirmed partial responses were seen in 10 patients with NSCLC and responses were maintained for between 2 and 26+ months. Seventeen patients, including 7 of the 10 NSCLC patients with partial responses, benefited from therapy and remained on study for 6 or more months. Responses and prolonged stable disease were seen across the 150- to 1000-mg dose range with no evidence of a dose-response, while the majority of dose interruptions and reductions due to toxicity occurred in patients receiving daily doses of >600 mg. Drug-related adverse events were also more severe in patients receiving >600 mg daily doses. In some patients with responding or stable disease, symptom relief (as measured by the Lung Cancer Scale (LCS) used in the Phase II trials) occurred by the first assessment, 2 weeks after beginning therapy.

3.2.2 Pharmacodynamic data

Pre- and post-IRESSA therapy skin biopsy data from 65 cancer patients enrolled in 2 Phase I trials (0011, 0012) found that after 1 month of therapy at all doses of 150 mg or greater, IRESSA profoundly inhibited EGFR activation. IRESSA also affected downstream EGFR-dependent pathway molecules including inhibition of MAP kinase activation while increasing expression of cyclin-dependent kinase inhibitors and maturation markers with resultant increased apoptosis (Albanell et al 2001).

3.2.3 Dose selection

Based on safety, pharmacologic, pharmacodynamic and anti-tumor activity data, 2 doses were subsequently selected for further investigation in the Phase II trials:

- The 250-mg dose was chosen to ensure adequate IRESSA exposure, as partial responses and prolonged disease stabilization were seen at doses of 150 mg and higher.
- The 500-mg dose was the highest dose shown to be well tolerated following chronic administration.
- The minimal (~ 30%) overlap in measures of steady state exposure allowed for potential discrimination between the 250-mg and 500-mg dose in comparative trials of efficacy and safety.
- Since both doses were below the 800- to 1000-mg dose at which dose-limiting toxicity occurred, a good safety margin was present.

4 EFFICACY RESULTS FROM RANDOMIZED PHASE II PROGRAM

4.1 Phase II trial design

4.1.1 Phase II trial design features and objectives

This program was designed to evaluate and compare 2 doses (250 mg, 500 mg) with respect to the efficacy and tolerability of IRESSA as treatment of patients with locally advanced or metastatic NSCLC who had previously received platinum-based chemotherapy. Pivotal data on the efficacy and safety of IRESSA were derived from Trial 0039, a randomized Phase II study conducted in the USA. Supportive data were obtained from a further randomized Phase II study, Trial 0016, conducted in Europe, Australia, South Africa, and Japan.

Trials 39 and 16 had almost identical objectives (Table 1). The efficacy objectives of both trials included the evaluation of objective tumor response and disease-related symptom improvement rates for 2 doses of IRESSA.

Table 1 Similarities of primary and secondary objectives in Trials 39 and 16

Objective class	Trial 0039	Trial 0016
Primary		
	Objective tumor response rate of IRESSA at both 250-mg and 500-mg daily doses	Same
	Disease-related symptom improvement rate	Safety profile characterization of 250 mg and 500 mg daily
Secondary		
	Estimate disease control rates	Same
	Estimate progression-free survival and overall survival	Same
	Estimate time to worsening of symptoms	Same
	Evaluate changes in QOL	Same
	Evaluate the demographic and pathophysiological factors affecting exposure to IRESSA	Same
	Further characterize the safety profiles of 250 mg and 500 mg IRESSA	Evaluate symptom improvement rates
		Evaluate potential differences between Japanese and non-Japanese patients; efficacy and safety, by dose and overall

An exploratory objective in both trials was to estimate the correlation between EGFR and probability of tumor response. At present, there is no established or validated method to measure EGFR expression in NSCLC tumor samples. In collaboration with another group, AstraZeneca is trying to establish such a method using immunohistochemical assessments but it appears likely that the method will require further work and time to develop. AstraZeneca is committed to examining this objective in the future and results will be communicated when available.

The pivotal Trial 0039 and supportive Trial 0016 shared the following trial design features and eligibility criteria:

- randomized, double-blind, parallel-group, Phase II multicenter trials
- advanced NSCLC patients who had previously received platinum-based chemotherapy

- histological confirmation of NSCLC
- at least 1 bi-dimensionally measurable lesion with clearly defined margins or nonmeasurable but evaluable disease at trial entry
- WHO performance status of 0 to 2

No upper age limit was imposed. The 2 trials, however, differed on several eligibility criteria captured in Table 2.

The patient population in Trial 0039 had more advanced and refractory disease as demonstrated by the larger number of patients with metastatic disease including more metastatic sites than patients in Trial 0016. While patients in both trials had disease-related symptoms, all patients in Trial 0039 were required to have disease-related symptoms as an eligibility criterion assessed by a validated scoring method in contrast to Trial 0016 where patients did not have to be symptomatic at trial entry. A score of ≤24 based on the LCS test (scoring ranges from 0 [severely symptomatic on all symptoms assessed] to 28 [symptom-free on all symptoms assessed]) contained in the Functional Assessment of Cancer Therapy – Lung (FACT-L) was used as a baseline eligibility criterion in Trial 0039 because this would allow a prospectively defined 2-point clinically significant symptom total score increase to occur in order to assess symptom improvement rates.

Table 2 Differences in eligibility criteria[a] in pivotal Trial 0039 and supportive Trial 0016

Trial 0039	Trial 0016
At least 2 chemotherapy regimens	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 (progressive disease [PD])	Considered recurrent or refractory
If PD, last dose of chemotherapy within 90 days prior to trial entry	
Symptomatic based upon an LCS score of ≤24[b]	
If CNS metastases, patients allowed within 1 to 2 weeks post-completion of definitive treatment	CNS metastases clinically and radiologically stable ≥2 months
	100 Japanese and 100 non-Japanese patients

[a] Due to the regulatory approval of docetaxel as a second-line treatment of advanced NSCLC, Trial 39 was designed as the pivotal registration trial in the US.
[b] Asymptomatic score is 28.

4.1.2 Phase II statistical considerations

Standard anti-tumor efficacy endpoints for NSCLC were adopted and methods for assessing and recording tumor response were applied consistently across all centers throughout the trials. Based on precedent, a 5% response rate was defined as the minimal acceptable level for anti-tumor activity in the setting where no effective therapy is available (Fleming 1982; Gehan 1961; Green and Dahlberg 1992; Simon 1987, 1989).

For Trial 0039, patients were randomized equally between 250 and 500 mg IRESSA. The 2 co-primary endpoints were the objective tumor response rate and symptom improvement rate, which were analyzed on an intent-to-treat basis. The trial was designed to independently evaluate each dose with the goal to test that the true rate for either or both co-primary endpoints is statistically greater than 5% at an overall 1-sided 2.5% significance level by Hochberg's procedure. The trial was sized to have power of .90 for a 1-sided .0125 significance level test that a given co-primary rate was ≤5% when the true rate was 15%. This required that 200 patients were to be randomized to obtain 100 patients per dose of IRESSA (Fleiss 1981).

For Trial 0016, the primary endpoint of the trial was the objective tumor response rate. Patients were randomized between 250-mg and 500-mg daily dose levels of IRESSA and stratified by ethnicity as Japanese versus non-Japanese. The trial was sized to independently evaluate the tumor response rate in the 4 strata defined by IRESSA dose and ethnicity. Within

each stratum, the goal was to have 90% power for a 2-sided 5% significance level test that the response rate was greater than 5% when the true response rate was 20%. This required a total of 45 patients evaluable for response per stratum. It was to be concluded that the response rate within a stratum was greater than 5% if there were at least 6 responses in 45 patients (13.3% observed rate, 95% exact confidence interval 5.1% to 26.8%). Assuming 10% of patients were not evaluable for response, a total of 100 Japanese patients and 100 non-Japanese patients were to be randomized to obtain 45 patients evaluable for response in each of the 4 strata.

Standard anti-tumor efficacy endpoints for NSCLC trials were adopted and methods for assessing and recording tumor response were applied consistently across all centers throughout the trials.

The criteria used to assess objective tumor response were based on the Southwest Oncology Group [SWOG] modification of the Union Internationale Contre le Cancer [UICC]/WHO criteria (Green and Weiss 1992). The patient's tumor status was classified as complete response (CR), partial response (PR), partial response in nonmeasurable disease (PRNM), stable/no response (SD), progression (PD), or unknown.

In the absence of measurable lesions, this applies only to patients with at least one of the following types of evaluable lesion:

- Radiographically assessable lesions with margins not clearly defined (eg, mediastinal lymph nodes, diffuse pulmonary infiltration)

Partial response constitutes improvement, which, in the investigator's opinion, unequivocally constitutes disease regression. No progression of other evaluable disease. No new lesions. All evaluable lesions and sites must be assessed using the same techniques as baseline.

For evaluable disease other than specified above, the only objective statuses that apply are CR, stable / no response, progression, and unknown.

4.2 Pivotal Trial 0039

4.2.1 Patients included in the analyses of efficacy

Overall, 221 patients from 30 centers in the US were randomized, of whom 216 were in the intent-to-treat (ITT) population of patients that received any trial treatment. Five patients were randomized but did not receive IRESSA treatment due to disease progression, a serious adverse event, or screening failure. Data from the ITT population only will be presented throughout this section. Unless otherwise stated, the data cutoff for efficacy data presented in this section was 1 August 2001 as described in the Integrated Summary of Efficacy (ISE).

4.2.2 Trial 0039 population characteristics

4.2.2.1 Demographic and disease characteristics

Patients were randomized to receive either the 250-mg dose or the 500-mg IRESSA dose. As expected, comparisons of demographic, disease, and prior treatment characteristics in the ITT group (patients who received at least 1 dose of trial therapy) showed no remarkable differences between treatment groups (Table 3, Table 4, and Table 5).

Table 3 Demographic characteristics, ITT population in Trial 0039

Characteristic	IRESSA dose		Total
	250 mg/day (N = 102)	500 mg/day (N = 114)	(N = 216)
Age (y)			
Mean (SD)	59.3 (11.0)	60.7 (10.3)	60.0 (10.7)
Median	61.0	62.0	61.0
Range	34 to 84	30 to 80	30 to 84
Age distribution (y), n (%)			
18-64	64 (62.7)	66 (57.9)	130 (60.2)
≥65	38 (37.3)	48 (42.1)	86 (39.8)
Sex, n (%)			
Male	60 (58.8)	63 (55.3)	123 (56.9)
Female	42 (41.2)	51 (44.7)	93 (43.1)
Origin, n (%)			
White	93 (91.2)	103 (90.4)	196 (90.7)
Black	3 (2.9)	4 (3.5)	7 (3.2)
Other[a]	6 (5.9)	7 (6.1)	13 (6.0)

[a] Includes Asian, Oriental, Hawaiian, Israeli, Taiwanese, and origin unreported

Table 4 Disease status at entry, ITT population in Trial 0039

Characteristic, n (%) of patients	IRESSA dose		Total
	250 mg/day (N = 102)	500 mg/day (N = 114)	(N = 216)
Disease type			
Measurable[a]	87 (85.3)	103 (90.4)	190 (88.0)
Nonmeasurable and evaluable[a]	15 (14.7)	11 (9.6)	26 (12.0)
WHO performance status			
0 (normal activity)	18 (17.6)	15 (13.2)	33 (15.3)
1 (restricted activity)	64 (62.7)	75 (65.8)	139 (64.4)
2 (in bed ≤50% of the time)	19 (18.6)	23 (20.2)	42 (19.4)
3 (in bed ≥50% of the time)	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 adenocarcinoma	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 tissue	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 [b]	11 (10.8)	16 (14.0)	27 (12.5)

[a] As defined by SWOG criteria.
[b] Includes sites of pleural and pericardial effusion.
ITT Intent to treat.
WHO World Health Organization.

Table 5 Previous cancer treatment, ITT population in Trial 0039

Characteristic	IRESSA dose		Total
	250 mg/day (N = 102)	500 mg/day (N = 114)	(N=216)
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)
Reason for discontinuation of most recent chemotherapy, n (%)			
Progressive disease	82 (80.4)	88 (77.2)	170 (78.7)
Unacceptable toxicity [a]	15 (14.7)	23 (20.2)	38 (17.6)
Completion of therapy	1 (1.0)	1 (0.9)	2 (0.9)
Other	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	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] Major reason for intolerability was platin and/or taxane therapy-induced peripheral neuropathy.

In the entire patient population only 2 patients had not received prior docetaxel therapy; all had received prior platinum therapy. A total of 141 patients were either refractory or intolerant of both docetaxel and platinum therapy. As defined by the inclusion criteria, prior regimens must have previously failed the patient because of progression on therapy or unacceptable toxicity. Patients who entered the trial due to disease progression on therapy had

to have documentation that their most recent dose of chemotherapy was within 90 days prior to this progression. These patients were almost equally distributed between the 2 doses (45% in the 250-mg dose group and 54% in the 500-mg dose group). A total of 185 patients had received 2 or more chemotherapy regimens or classes of agents, which were discontinued for progressive disease or intolerance or required re-institution of different chemotherapy within 90 days of elective therapy cessation.

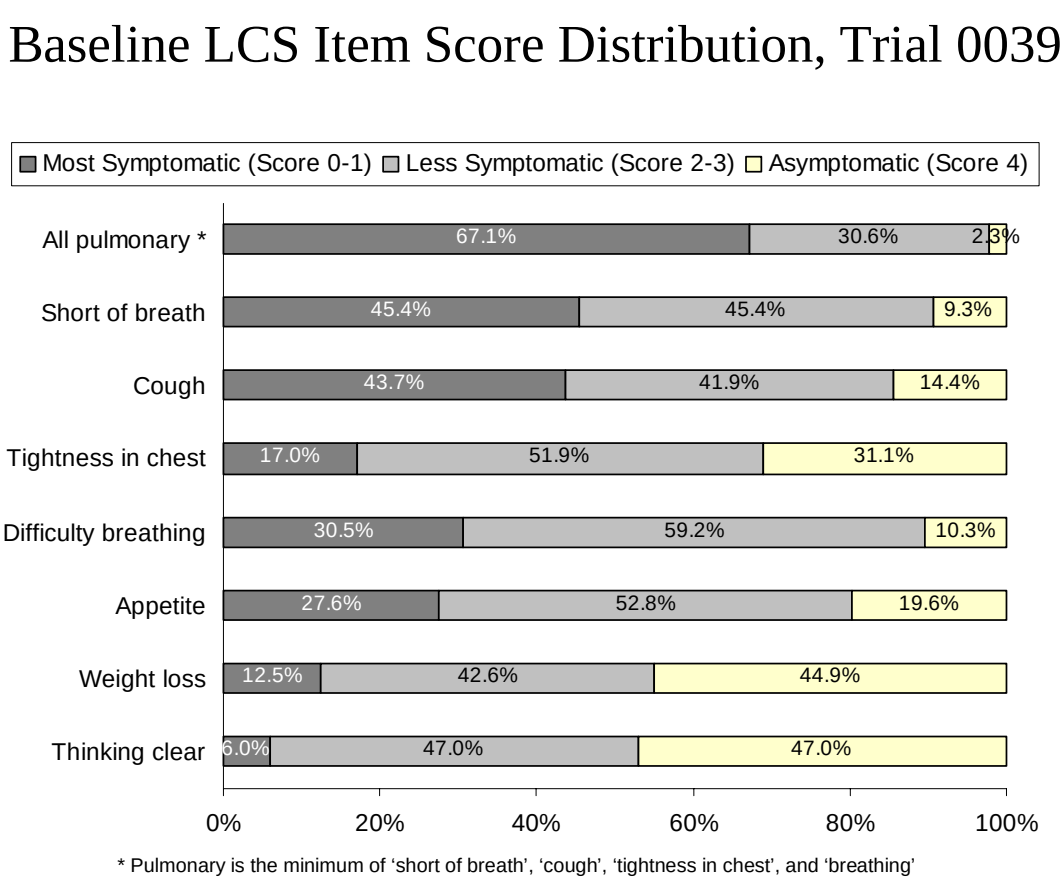
Comparisons of clinical and treatment characteristics at trial entry showed that they were well balanced across both patient groups. The demographic and disease profile was similar to the patient profile in newly diagnosed patients with advanced disease with the exception of a higher frequency of adenocarcinoma histology and brain metastases. As expected due to eligibility criteria, patients were heavily pretreated with almost one-half having had 3 or 4 prior regimens, three-quarters having had both taxanes, and the majority having had radiation. All but 2 patients (214/216) received prior docetaxel and all patients received prior platinum-based therapy. Only 1 patient received less than 2 prior therapies. Out of the 216 patients in the ITT population, 170 patients entered the trial because of progressive disease within 90 days of their last chemotherapy dose and 38 patients entered because of unacceptable toxicity from their previous chemotherapy. Only 8 patients entered the trial for reasons other than unacceptable toxicity or disease progression. Median time from diagnosis was greater than median survival time in newly diagnosed patients.

4.2.2.2 LCS baseline characteristics

The baselines distribution of each LCS item by score for all patients is presented in Figure 1. The median LCS score was 16 and was identical in both dose groups as was median LCS score by performance status, current disease status, and number of prior regimens.

The median LCS score in Trial 0016 evaluable subset is higher, ie, better than in Trial 0039. In the first-line setting, patients with Stage IIIB and IV disease entering ECOG 5592 had a median LCS score of 20.5 if PS 0 and 17.9 in PS 1 (Cella et al 2002). Thus, it is not unexpected that the median LCS scores at trial entry were 16 in Trial 0039 (third-line plus treatment) and 18 in Trial 0016 (second and third-line treatment; see Section 4.3.2.2).

Figure 1 Disease-related symptom distribution at baseline by score for all patients



* Pulmonary is the minimum of 'short of breath', 'cough', 'tightness in chest', and 'breathing'

With respect to each of the 7 individual symptoms, frequency and severity were balanced across both arms. Shortness of breath was the most frequently reported pulmonary symptom, which was most severe in the greatest number of patients. Closely following shortness of breath with respect to frequency and severity was cough and difficulty breathing. Of the 3 symptoms due to advanced cancer, poor appetite was the most frequent and severe, but was less frequent and severe than the 3 pulmonary symptoms.

4.2.3 Demonstrated efficacy benefits in Trial 0039

4.2.3.1 Objective tumor response

The rate of investigator-assessed objective tumor response using the SWOG modification of the UICC/WHO criteria (Green and Weiss 1992) was a primary endpoint. This criterion allowed inclusion of patients with non-measurable but evaluable lung disease.

Objective tumor responses were seen at both doses. The objective tumor response rate was 11.8% in the 250-mg/day group and 8.8% in the 500-mg/day group (Table 6).

Table 6 Objective response rates in pivotal Trial 0039

Parameter	IRESSA dose 250 mg (N = 102)	IRESSA dose 500 mg (N = 114)
Number of patients with tumor response [n, (%)]	12 (11.8)	10 (8.8)
(95% confidence interval)	(6.20 to 19.7)	(4.3 to 15.5)
p-value (one-sided)	0.005	0.0599
PR	9	9
PRNM	3	1
Number of patients with SD [n, (%)]	31 (30.4)	31 (27.2)
Number of patients with PR, PRNM, or SD	43 (42.2)	41 (36.0)
(95% confidence interval)	(32.4 to 52.3)	(27.2 to 45.5)

PR Partial response.
PRNM Partial response in patient with non-measurable disease only.
SD Stable disease.

The majority of tumor responses (77.3%, 17/22) were ongoing at the time of data cutoff (minimum follow-up of 4 months, maximum follow-up of 9 months). The median duration of tumor response could not be calculated for the 250-mg/day group (10 of the 12 patients had not progressed); the median duration of tumor response for the 500-mg/day group was estimated at approximately 4.5 months. As of the 1 August 2001 data cutoff date for the ISE, the range of duration of tumor response was 1+ to 7+ months in the 250-mg/day group and 2+ to 4+ months in the 500-mg/day group. With an additional 5 months of follow-up as of a cutoff date of 31 December 2001, the range of duration of tumor response in the 250-mg/day group had increased to 3+ to 8+ months and to 3+ to 7+ months in the 500-mg/day group. Notably, the majority of responding patients (72.7%, 16/22) were treated longer with IRESSA than the time interval of their most recent chemotherapy.

For both doses combined, the majority of objective partial responses (72.2%, 13 of 18 with measurable disease) occurred in bulky tumors with total areas >10 cm^2, and tumor size reduction occurred in the lung and extra pulmonary metastatic sites. Responses were seen in approximately two-thirds of responding patients at the first assessment (Week 4) while the remaining one-third of responses occurred by 16 weeks. Response rates were seen whether patients had had 2 (7.9%, 7/89), 3 (9.7%, 7/72), or 4 or more (15.1%, 8/53) prior treatment regimens.

Evaluation of baseline characteristics in relation to response found responses even in patients with lung cancer often refractory to chemotherapy including performance status of 2 and non-measurable, evaluable disease. Responses occurred in both men and women but occurred more often in women (19.4%, 18/93) than men (3.2%, 4/123). Responses occurred in all histologies, but occurred more often in adenocarcinomas (13.3%, 19/143) than in squamous (6.3%, 2/32) or other histologies (2.5%, 1/40).

4.2.3.2 Disease-related symptom improvement

The 7-symptom LCS component, or the L-component of the FACT-L instrument, was used to assess disease-related symptoms (Cella et al 1995). The FACT-L, including the LCS, is a validated, reliable, sensitive assessment tool available in multiple languages for which group-minimal clinically significant score change has been defined as 2 points or more based on large trials in advanced NSCLC. A 2- or 3-point change in the LCS was found anchored to performance status, weight loss, response, and time to progression (Cella et al 2002). 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.

Weekly assessments consistent with the design of the questionnaire were used. Changes from baseline in the LCS score were assessed at each weekly 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.

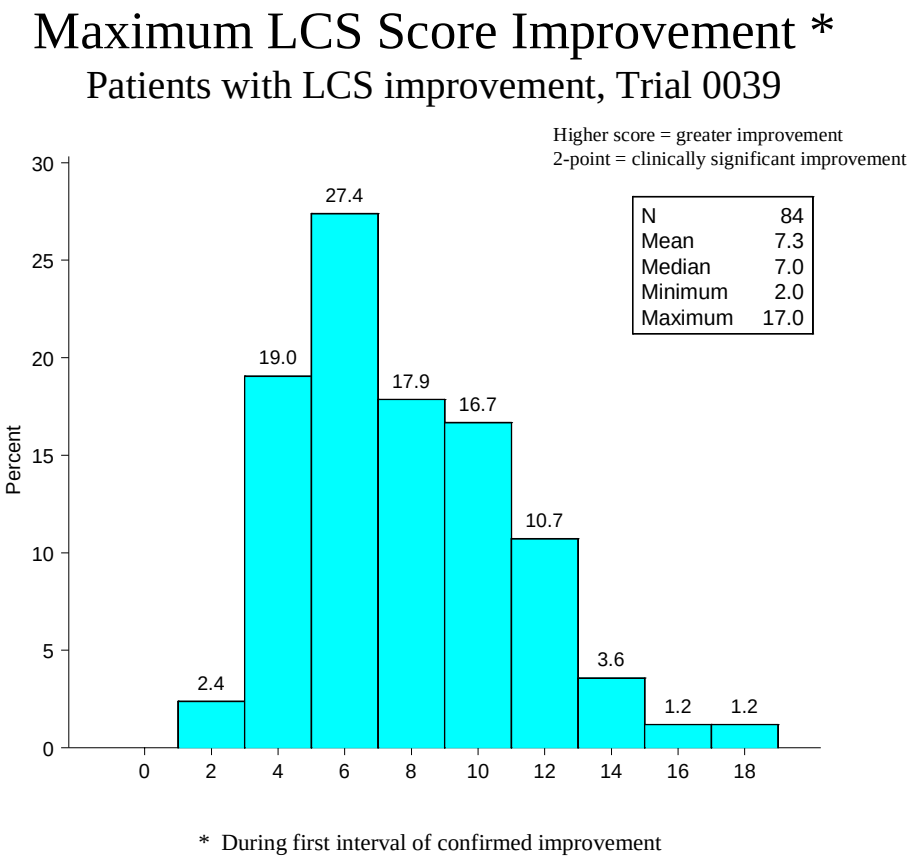
The overall compliance (percentage of weekly assessments received) was 84% allowing robust conclusions; there was no apparent difference in compliance between the doses.

As shown in Table 7, the symptom improvement rates in the trial were similar for the 2 dose groups, significantly greater than 5%, (1-sided p-value <0.0001), and rapid. Of the 84 patients who had symptom improvement, the maximum LCS scores improved by a median of 7.0 points with a range of 2.0 to 17.0 (Figure 2).

Table 7 Rate of disease-related symptom improvements in Trial 0039

	IRESSA dose assignment	
Parameter	**250 mg/day (N = 102)**	**500 mg/day (N = 114)**
Number of patients with symptom improvement	44	40
Rate of response (%) (95% confidence interval) p-value (1-sided)	43.1 (33.4 to 53.3) <0.0001	35.1 (26.4 to 44.6) <0.0001
Median time to improvement, days	10.0	9.0

Figure 2 **Maximum LCS score improvement in patients who had disease-related symptom improvement**



* During first interval of confirmed improvement

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. In the 500-mg/day group, 80% (32/40) of patients were still showing an improvement at data cutoff.

The symptom improvement rates 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).

In a written communication from the FDA, identification of patients with ≥2-point (maximal 4 point) improvement in each of the pulmonary symptoms was requested. Patients with a baseline symptom score of 3 or 4 for a specific symptom could not have a 2-point improvement, so the number of evaluable patients could and did vary with respect to each of the different symptoms.

Overall, 12% to 20% of patients in the 250 mg/day treatment group and 10% to 15% of patients in the 500 mg/day treatment group showed a ≥ 2 point improvement in 1 or more of the pulmonary symptoms listed above. A patient could improve in 1, 2, 3, or all 4 of the symptoms. Use of concomitant medications may have contributed to this result in only a small proportion of patients.

4.2.3.3 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 number of progression-free survival days was similar between the 2 dose groups: 1.9 months (95% CI: 1.8, 2.8) for the 250-mg/day group and 2.0 months (95% CI: 1.6, 2.2) for the 500-mg/day group.

4.2.3.4 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, approximately 6.0 months in each dose group. As of 31 December 2001, 52 (51.0%) of the patients in the 250-mg/day group were alive compared to 34 (29.8%) of the patients in the 500-mg/day group. The median survival was approximately 6.5 months in the 250-mg/day group and 5.9 months in the 500-mg/day group.

4.2.3.5 QOL (FACT-L)

The FACT-L questionnaire contains 5 different domains: disease-related symptoms, physical, functional, emotional, and social. The FACT-L was collected monthly. A significant change was defined as a 6-point difference (Cella et al 2002).

There were no significant differences in median baseline scores between the different groups for FACT-L; baseline scores confirmed compromised QOL. The overall compliance was 86% of all forms received, allowing robust conclusions.

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%).
- Time to FACT-L improvement was similar for each dose group with medians ranging from from 29-31 days.
- 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 FACT-L.

4.2.3.6 Relationship between endpoints

Exploratory analyses were performed to examine interrelationships between tumor response, disease-related symptom improvement, and survival.

Twenty-one out of 22 patients (95.5%) who showed a tumor response also showed an improvement in disease-related symptoms; 71.0% of patients with stable disease (44/62) and 16.8% (19/113) of patients with PD had improved LCS scores.

Patients with partial remissions had better survival than patients with stable disease while patients with progressive disease had poorest survival. All patients who experienced a tumor response were alive at the data cutoff. Patients with disease-related symptom improvement appeared to have longer survival regardless of objective tumor response.

4.2.3.7 Subgroup analyses

In Trial 0039, the finding of higher objective and symptom improvement rates in women than men, and to a lesser extent, adenocarcinoma histology was an unanticipated observation. The explanation for this observation is unknown. Comparison of men and women with respect to baseline disease and prior treatment history showed overall comparability with the exception of histology as 79% of women had adenocarcinoma histology compared to 58% of men. Comparison of pharmacokinetic parameters between men and women revealed no significant differences. The current study was not designed or adequately sized to definitively explore this observation. While men did less well than women in this trial, nonetheless objective responses did occur and one-third of men had sustained symptom improvement. To fully evaluate these observations, further clinical investigations will be required.

4.3 Supportive Trial 0016

4.3.1 Patients included in the efficacy analyses

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 IRESSA treatment due to a screening failure.

Of the 209 patients treated (ITT population), 208 were considered evaluable for response and 140 who had both completed a baseline questionnaire and had a LCS score of 24 or less were considered evaluable for symptom improvement. Data based on the ITT population will be presented in Sections 4.3.2.1, 4.3.3.3, and 4.3.3.4; data based on the evaluable for response population will be presented in Sections 4.3.3.1 and 4.3.3.5; and data based on the evaluable for symptom improvement population will be presented in Sections 4.3.2.2 and 4.3.3.2.

4.3.2 Trial 0016 population characteristics

4.3.2.1 Demographic and disease characteristics at baseline

Patients were randomized between 250-mg and 500-mg IRESSA dose levels. As expected, comparisons of demographic, disease, and prior treatment characteristics in the ITT group (patients who received at least 1 dose of trial therapy) showed no remarkable differences

between treatment groups (Table 8). As a consequence of differing eligibility requirements, the patient population in Trial 0016 compared to that in Trial 0039 was less intensively treated with chemotherapy, had a shorter median time from diagnosis to study entry, and had lower overall tumor burden.

Table 8 Demographic characteristics of ITT patients in Trial 0016

Demographic characteristics	**Randomized treatment**		
	IRESSA 250 mg/day (n=104)	**IRESSA 500 mg/day (n=106)**	**All patients (n=210)**
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[a]	0	1 (0.9)	1 (0.5)

[a] Maltese.

The disease characteristics of patients at trial entry are presented in Table 9.

Table 9 Disease characteristics of ITT patients at trial entry in Trial 0016

Characteristics	Randomized treatment		
	IRESSA 250 mg/day (n=104)	**IRESSA 500 mg/day (n=106)**	**All patients (n=210)**
Previous cancer treatment, n (%)			
1 previous chemotherapy regimen	104 (100.0)	106 (100.0)	210 (100.0)
2 previous chemotherapy regimens	46 (44.2)	46 (43.4)	92 (43.8)
Radiotherapy	52 (50.0)	48 (45.3)	100 (47.6)
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)

Table 9 Disease characteristics of ITT patients at trial entry in Trial 0016 (continued)

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

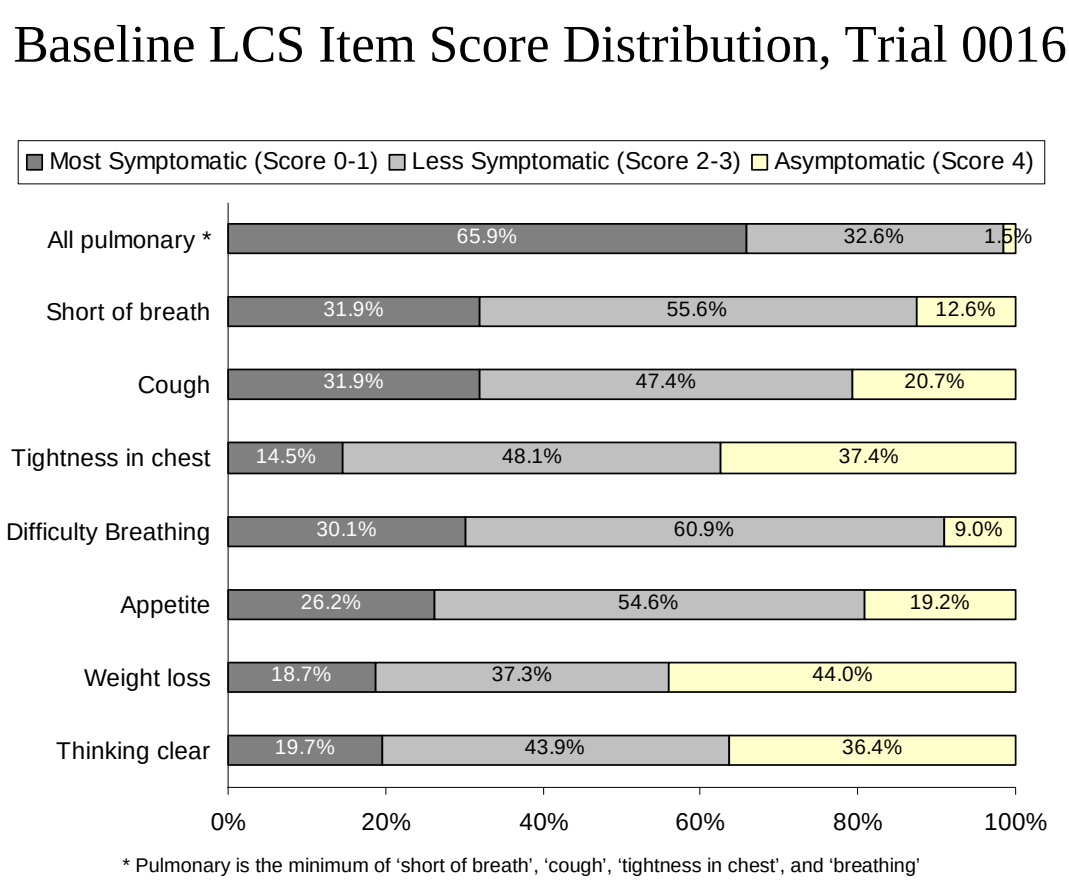
[a] Includes sites of pleural and pericardial effusion.
WHO World Health Organization

4.3.2.2 LCS baseline characteristics

For Trial 0016, 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 0039), analysis of the subset of the per-protocol population who completed baseline FACT-L and had a baseline LCS score of 24 or less was done. A total of 160 patients had a baseline LCS score of which 140 (87.5%) comprised the evaluable for symptom improvement population with a value of 24 or less, 67 in the 250-mg/day group and 73 in the 500-mg/day group.

Overall, median baseline scores for LCS were 18.0 for the 2 dose groups indicating that evaluable patients were a symptomatic population (Figure 3).

Figure 3 Disease-related symptom distribution at baseline by score for all patients



* Pulmonary is the minimum of 'short of breath', 'cough', 'tightness in chest', and 'breathing'

Patients who had metastatic disease at trial entry were more symptomatic than patients with locally advanced disease. Both dose groups were comparable with respect to frequency and severity of each of disease-related symptom. The most frequent symptoms as well as symptoms with the greatest severity were difficulty breathing, shortness of breath and cough although poor appetite and cough were almost identical. As expected in this patient population, the majority of patients (65.7%, 92/140) in both dose groups had at least 1 serious (most symptomatic) pulmonary symptom at baseline.

Comparison of individual baseline disease related symptom frequency and severity in the evaluable subpopulation in Trial 0016 is remarkably similar to that of patients in Trial 0039 although patients in Trial 0039 were slightly more symptomatic with shortness of breath and coughing.

4.3.3 Demonstrated efficacy benefits in Trial 0016

4.3.3.1 Objective tumor response

Objective tumor response rate for the 250-mg/day group was 18.4% and was 19.0% for the 500-mg group (Table 10). The majority of tumor responses were achieved by Week 4, and objective responses were seen regardless of whether 1 or 2 prior regimens had been received.

Table 10 Investigator's assessment of best overall objective response: evaluable for response population

Best tumor resonse	IRESSA dose 250 mg (N = 103)	IRESSA dose 500 mg (N = 106)
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)

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 (17.9%, 21/117) or 2 previous regimens (19.8%, 18/91) 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). Responses occurred in 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.

More women experienced tumor responses at both the 250-mg/day and the 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 this trial, where approximately one-half of the patients were Japanese, higher tumor response rates were seen in Japanese patients in both the 250-mg/day dose group and the 500-mg/day group (25.5% and 26.4%, respectively) than for non-Japanese patients (10.4% and 11.5%, respectively). This observation is discussed further in Section 4.4.

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 (minimum duration of follow-up 4 months, maximum duration of follow-up 8 months).

4.3.3.2 Disease-related symptom improvement

The overall compliance for evaluable patients with respect to the weekly disease-related symptom questionnaire (LCS) was 74% (percentage of weekly assessments received). There was no apparent difference in compliance across the doses although higher compliance was associated with a performance status of 0 or 1 (vs PS 2), second-line (vs third-line), and Japanese (vs non-Japanese) patients.

The disease-related symptom improvement rate data are summarized in Table 11. The symptom improvement rates were similar for the 2 dose groups. Of the 54 patients who had symptom improvement, the maximum LCS improvement had a median of 7.0 points with a range of 3.0 to 17.0.

Table 11 Rate of disease-related symptom improvements: evaluable for symptom improvement per LCS population

	IRESSA dose assignment	
Parameter	**250 mg/day (N = 67)**	**500 mg/day (N = 73)**
Number of patients with symptom improvement	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

The time to disease-related symptom improvement was similar for each dose group with a median time to symptom improvement of 8 days in both dose groups. In the 250-mg/day group, 81% (22/27) of patients who had an improvement were still showing an improvement at the data cutoff. In the 500-mg/day group, 63% (17/27) of patients were still showing an improvement at data cutoff.

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 a written communication from the FDA, identification of patients with ≥2-point (maximal 4 point) improvement in each of the pulmonary symptoms was requested. Not all patients could have had a 2 point improvement because of a specific symptom score of 3 or 4, therefore the number of evaluable patients could and did vary with respect to each of the different symptoms.

In both the treatment groups, improvement in each of the disease-related pulmonary symptoms was seen for the entire patient group. Overall, 6% to 20% of patients in the 250-mg/day treatment group and 12% to 23% of patients in the 500 mg/day treatment group showed a ≥ 2 point improvement in 1 or more of the pulmonary symptoms listed above. A patient could improve in 1, 2, 3, or all 4 of the symptoms.

4.3.3.3 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 number of progression-free survival days was similar for the 2 dose groups: 2.8 months (95% CI: 2.0, 2.9) for the 250-mg/day group, and 2.8 months (95% CI: 2.0, 3.9) for 500 mg/day group.

4.3.3.4 Overall survival

The primary analysis population for overall survival was the ITT population.

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; the median survival could not be estimated.

4.3.3.5 QOL (FACT-L)

For Trial 0016, the primary analysis for QOL was based on the evaluable-for-response population.

Median baseline scores for the 2 doses for FACT-L ranged from 85.0 to 87.8.

Summary of QOL findings:

- FACT-L improvement rate was similar for the 2 dose groups; 23.9% (95% CI: 14.3%, 35.9%) for the 250-mg/day group, and 21.9% (95% CI: 13.1%, 33.1%) for the 500-mg/day group.

- FACT-L improvement occurred by 30 days for 54% of the patients in the 250-mg dose group, increasing to 97% of the patients by 60 days. In the 500-mg dose group, FACT-L improvement occurred by 30 days for 50% of the patients, with 92% of the patients having FACT-L improvement by 60 days.

- 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 FACT-L.

4.3.3.6 Relationship between disease-related symptoms and objective tumor response

Exploratory analyses were performed to examine interrelationships between tumor, disease-related symptom improvement, and survival.

4.3.3.6.1 Disease-related symptom improvement and tumor response

Out of the 39 patients with objective tumor response, disease-related symptom improvement could not be assessed for 12 patients who were not included in the evaluable for symptom improvement population. The majority of patients (77.8%) with objective tumor response had symptom improvement. More than half (53.3%) of patients with stable disease had symptom improvement. Of the patients with progressive disease, 13.2% had improvement in disease-related symptoms.

4.3.3.6.2 Tumor response and survival

All patients who experienced a tumor response were alive at the data cutoff.

4.3.3.6.3 Disease-related symptom improvement and survival

At the data cutoff, 81% (44/54) of patients with symptom improvement and 62% (44/71) of patients without symptom improvement were alive. Patients with disease-related symptom improvement appeared to have longer survival regardless of objective tumor response.

4.3.3.7 Subgroup analyses

Efficacy between Japanese and non-Japanese patients was more fully evaluated in Trial 0016 as a prospective protocol objective. 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 was 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. Comparison of pharmacokinetic parameters between Japanese and non-Japanese patients revealed no significant differences. The results regarding a potential ethnic difference were inconclusive due to the non-randomized comparison, and the limitations of the data. However, 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. To fully evaluate these observations, further clinical investigations will be required.

4.4 Efficacy conclusions

Two large, concurrently conducted, double blind Phase II trials in over 400 patients preceded by a large Phase I program have consistently demonstrated modest but reproducible and durable objective tumor responses ranging from 8.8 to 19.0%. Both responses and stable disease are especially notable in light of stringent eligibility requirements in Trial 0039 which required not only the previous use of 2 proven effective chemotherapy agents, but also documented disease progression within previous 90 days or therapy intolerance. Two-thirds of patients in this trial were refractory to both platinum and docetaxel and approximately 85% were refractory to 2 or more regimens. Anti-tumor activity was at least as large to that seen with conventional single agent chemotherapy in the recurrent setting in this disease. As expected, survival was best in patients with responses, intermediate in patients with stable disease and worst in patients with progressive disease.

The second measure of efficacy was that of symptom improvement measured weekly using a validated, reliable instrument. Methodologic procedures included the prospective use of defined criteria for clinically meaningful improvement and inclusion of required duration of improvement for at least 4 weeks. Interpretation of symptomatic response from previous studies has been hampered by poor compliance to completion of questionnaires, clinical deterioration, or both. The especially high compliance rate found in the pivotal trial provides increased confidence in the observed results. The requirement of a specified minimum duration of 1 month reduces potential for placebo effect. With this in mind, the similar rates

of symptom improvement between Trials 0039 and 0016 was remarkable. Coupled with the amount of overall and individual symptom improvement in the absence of other significant, potentially contributory therapeutic intervention is compelling evidence of patient perceived and experienced benefit.

The high degree of correlation of symptom improvement of approximately 95% and 87% in Trials 0039 and 0016 with radiographic response is logical on a purely anatomic basis as predominant disease-related symptoms are pulmonary and they are caused by obstruction, compression, or loss of pulmonary tissue by tumor. The correlation of symptom improvement with stable disease is also reasonable as stable disease is a continuum of tumor reduction with up to 49% tumor reduction of measurable, evaluable disease. Similar findings with incidence of disease-related symptom relief exceeding response rates in approximately the same ratio as in these studies have been repeatedly observed in serial assessments of patients with newly diagnosed non-small cell lung cancer receiving effective chemotherapy. Improvement in quality of life in one-quarter of patients is further substantiation and supportive of patient benefit.

The key component of the randomization in these trials was to determine whether or not there was a dose-dependent difference in efficacy. Both trials clearly demonstrated no difference in efficacy between the 250-mg or 500-mg daily dose.

In sum, efficacy demonstrated in this trial is clinically significant, compelling, and highly relevant to the patient population.

5 SAFETY RESULTS PHASE II PROGRAM

5.1 Background – Phase I trial safety data

Animal toxicology identified the following body systems with EGFR-dependent tissue for special monitoring during clinical evaluation: skin, corneal epithelium, gastrointestinal system, liver, renal papilla, and cardiac conduction (prolongation of PR interval). The Phase I program (Trials 0005, 0011, 0012, and V-15-11) was unusually large and included a total of 252 patients with solid tumors (including 100 patients with NSCLC). At IRESSA doses >250 mg, 27 patients were exposed for 3 to 6 months and an additional 17 patients for greater than 6 months.

Dose-related frequency and severity was seen with diarrhea and skin rash or acne. Gastrointestinal changes (diarrhea, nausea, vomiting) and skin changes (rash, acne, dry skin, pruritis) were common and expected consequences of the pharmacological action of EGFR-TK inhibition. Grade 3 diarrhea was dose limiting at daily doses of 800 mg and 1000 mg. Patients in these trials had intensive monitoring for PR interval prolongation and corneal epithelium changes by means of ECGs and slit lamp evaluations performed every 1 to 2 weeks for a total of over 7000 evaluations. Infrequently, patients had symptomatic reversible corneal erosion, sometimes in association with aberrant eyelash growth. Neither routine, serial slit lamp evaluations or serial ECGs were found to be of any clinical utility. Liver transaminase

elevation and renal dysfunction or hematuria, were uncommon or rare, and inconsistently seen at the different doses. As anticipated, there was no data to suggest unanticipated new, unusual, or life-threatening toxicity or exacerbation of any previous chemotherapy-induced toxicity.

As a result, in pivotal Trial 0039 and supportive Trial 0016, ECGs and ophthalmologic examinations were required only at baseline and at the time of withdrawal in the absence of any clinical indication to confirm Phase I findings. In addition, eligibility criteria with respect to bone marrow, renal, and liver function were liberalized, wearing of contact lenses was allowed, and restrictions on co-morbid ophthalmologic conditions and cardiac conduction disorders were removed. Thus, safety monitoring could be modest and similar to that done as routine as best clinical practice in patients with advanced NSCLC cancer not receiving intensive chemotherapy.

5.2 Patients included in the analyses of safety

A total of 960 subjects (714 cancer patients, and 246 healthy volunteers) were exposed to IRESSA in the 20 completed trials included in the NDA submission.

The 20 completed monotherapy trials included are as follows:

- 2 Phase II trials conducted in patients with advanced NSCLC (pivotal Trial 0039, and supportive Trial 0016)

- 6 Phase I trials conducted in patients with various solid tumors, including NSCLC (0005, 0011, 0012, 0035, 0038, and V-15-11)

- 12 Phase I trials conducted in healthy male volunteers (0001, 0002, 0003, 0010, 0027, 0028, 0030, 0031, 0033, 0034, 0036, and 0051)

The number of subjects exposed to each dose of IRESSA, and the durations of exposure, were appropriate for the evaluation of safety at a recommended oral dose of 250 mg/day. A total of 420 subjects (297 cancer patients, and 123 healthy volunteers) were exposed to single-doses of IRESSA between 225 and 300 mg/day, with a maximum duration of dosing of 506 days.

The cutoff dates for safety data included in this section and the Integrated Summary of Safety Information (ISS) was 1 August 1 2001. All safety data and adverse events that occurred on or before this date are included in this document. The data cutoff date for the 4-Month Safety Update Report (4-MSU) was 1 March 2002. Safety data presented in this document are not taken from the 4-MSU.

Safety data from ongoing clinical trials with IRESSA were summarized in the 4-MSU (see Section 5.9).

In addition, a large safety database is available in patients with advanced NSCLC who have already received or cannot receive standard therapy. At the time of the 4 month safety update, slightly under 10,000 patients with advanced NSCLC had been exposed to 250 mg daily

IRESSA on the Expanded Access Program (EAP). As of August 2002, over 20,000 patients have been exposed to IRESSA on EAP and one-half of these patients have received IRESSA for 6 or more months. All serious adverse events (SAE) from the EAP, including deaths, have been reported directly to the US IND and other health authorities according to local regulations. With the exception of 2 patients who had a type of rare skin toxicity also reported rarely with many other drugs and 1 potential drug-drug interaction detailed in Section 5.10, the relative paucity of unexpected, related serious adverse events reported in a patient population similar to the data detailed in the current submission, confirms the low toxicity and safety data. Thus, other than the previously noted exceptions, safety data from the EAP are excluded from the analyses and subsequent summary sections.

5.3 Exposure to IRESSA

5.3.1 Duration of treatment

Duration of exposure in Trials 0039 and 0016 based on the data cutoff date of the ISS (1 August 2001) is summarized in Table 12. For both dose groups in both trials, the mean number of days on treatment was similar to the mean number of days on trial, suggesting that there were few interruptions in trial treatment. The duration of treatment was generally longer in Trial 0016 than in Trial 0039.

Table 12 Duration on trial and duration of treatment[a]

Category	Pivotal Trial 0039		Supportive Trial 0016	
	250 mg (n=102)	500 mg (n=114)	250 mg (n=103)	500 mg (n=106)
Number of days on trial				
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				
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] The follow-up period was 4 months after the last patient entered the trial.

After Trial 0039 closed on 17 December 2001, patients who continued to benefit from IRESSA were subsequently enrolled in the open extension Trial 0026. Patients' exposure to

IRESSA in Trials 0039 and 0016 has increased since the data cutoff dates used for the ISS with an additional 57 patients having been exposed to IRESSA for >6 months. The 4-MSU provided an additional 5 months exposure for the patients remaining on these 2 studies, which did not change the safety profile, adverse event frequency, overall safety conclusions provided in the ISS.

5.3.2 Dose interruptions and dose reductions due to toxicity

In Trials 0039 and 0016 (which were both blinded with respect to dose), IRESSA treatment could be temporarily delayed or withdrawn for up to 14 days in the event of:

- skin rash that was unacceptable to the patient
- Common Toxicity Criteria (CTC) Grade 3 or 4 diarrhea
- corneal erosion, ocular infection, or inflammation
- other unanticipated, drug-related CTC Grade 3 or 4 toxicity
- Only 1 dose reduction (ie, 2 tablets to 1 tablet) due to unacceptable toxicity was allowed per patient. The dose reduction was from 500 to 250 mg, or from 250 mg to 100 mg, depending upon the original dose assignment.

Table 13 summarizes the number of patients in Trials 0039 and 0016 who had interruptions in therapy or dose reductions due to toxicity.

Table 13 Number (%) of patients with dose 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	11 (10.4)

In both trials, the proportion of patients who had interruptions in therapy was lower in the 250-mg/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.

5.4 Evaluation of adverse events in Trial 0039

5.4.1 Overview of adverse events

Nearly all patients (98.6%) in Trial 0039 had at least 1 adverse event. The majority of patients (79.2%) had at least 1 adverse event that was considered by the investigator to be drug-related. The percentage of patients who had drug-related events was lower in the 250-mg/day group than in the 500-mg/day group (72.5% versus 85.1%). The incidence of drug-related serious adverse events was low in both treatment groups. Overall, the 250-mg dose was better tolerated than the 500-mg dose.

The number of patients with adverse events falling within each principal category (adverse events leading to death, adverse events leading to withdrawal, serious adverse events, and CTC Grade 3 or 4 adverse events) from Trial 0039 is summarized in Table 14. Adverse events are reported by the dose of IRESSA received at trial entry.

Table 14 Overview of adverse events in Trial 0039

Category[a]	**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	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)

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

5.4.2 Adverse events

The most frequent adverse events experienced by ≥25% of patients receiving IRESSA 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 IRESSA 250 mg/day than patients receiving 500 mg/day.

Adverse events with an incidence of ≥10% in either dose group are presented in Table 15.

Table 15 Adverse events with an incidence of ≥10% in Trial 0039

Adverse event (COSTART term)[a]	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[b] (10.8)	16[b] (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)

[a]A patient may have had more than 1 adverse event.
[b]Predominantly common cold and upper respiratory tract infections.
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

Many of the adverse events listed in Table 15, such as asthenia, dyspnea, increased cough, and pain, are consistent with advanced lung cancer.

5.4.2.1 Drug-related adverse events

Drug-related adverse events (as determined by the investigator) with an incidence of ≥5% in either dose group are presented in Table 16.

The most frequent drug-related adverse events experienced by ≥10% of patients receiving IRESSA 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 IRESSA 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 1 or 2, and the safety profile of IRESSA did not appear to change with chronic dosing (up to a maximum of nearly 8 months of treatment).

Table 16 Drug-related adverse events with an incidence of ≥5% in Trial 0039

Drug-related adverse event (COSTART term) [a]	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)

[a] A patient may have had more than 1 adverse event.
COSTART Coding Symbols for Thesaurus of Adverse Reaction Teerror!

5.4.2.2 Adverse events with CTC Grades 3 or 4

Thirteen (12.7%) patients at the IRESSA 250-mg/day dose had CTC Grade 4 adverse events compared to 20 (17.5%) at 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 was the only drug-related adverse event of CTC Grade 3 or 4 severity with an incidence of ≥5% in either dose group (500-mg/day dose group, Table 17 and Table 18).

Table 17 Drug-related adverse events of ≥5% by CTC Grade in the 250 mg/day dose group, Trial 0039

Adverse event (COSTART term)[a]	Number (%) of patients (N = 102)				
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	49 (48.0)	42 (41.2)	6 (5.9)	1 (1.0)	0
Rash	43 (42.2)	40 (39.2)	4 (3.9)	0	0
Acne	25 (24.5)	19 (18.6)	6 (5.9)	0	0
Dry skin	13 (12.7)	12 (11.8)	1 (1.0)	0	0
Nausea	13 (12.7)	7 (6.9)	5 (4.9)	1 (1.0)	0
Vomiting	12 (11.8)	9 (8.8)	2 (2.0)	1 (1.0)	0
Anorexia	7 (6.9)	3 (2.9)	4 (3.9)	0	0
Pruritus	8 (7.8)	7 (6.9)	1 (1.0)	0	0
Asthenia	6 (5.9)	2 (2.0)	2 (2.0)	1 (1.0)	1 (1.0)

[a] A patient may have had more than 1 adverse event.
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.
CTC Common Toxicity Criteria.

Table 18 Drug-related adverse events of ≥5% by CTC Grade in the 500 mg/day dose group, Trial 0039

Adverse event (COSTART term)[a]	Number (%) of patients (N = 114)				
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	76 (66.7)	51 (44.7)	19 (16.7)	6 (5.3)	0
Rash	61 (53.5)	41 (36.0)	17 (14.9)	3 (2.6)	0
Acne	37 (32.5)	21 (18.4)	12 (10.5)	4 (3.5)	0
Dry skin	30 (26.3)	27 (23.7)	3 (2.6)	0	0
Nausea	20 (17.6)	12 (10.5)	7 (6.1)	1 (0.9)	0
Vomiting	10 (8.8)	6 (5.3)	1 (0.9)	3 (2.6)	0
Anorexia	10 (8.8)	7 (6.1)	3 (2.6)	0	0
Pruritus	10 (8.8)	7 (6.1)	2 (1.8)	1 (0.9)	0
Weight loss	6 (5.2)	4 (3.5)	2 (1.8)	0	0

[a] A patient may have had more than 1 adverse event.
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.
CTC Common Toxicity Criteria.

5.4.3 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 19.

Twenty-two patients (21.6%) in the 250-mg/day dose group died during treatment or post treatment (ie, within 30 days after the last dose of IRESSA) compared to 27 patients (23.7%) in the 500-mg/day group.

Six patients (5.9%) in the 250-mg/day dose group had adverse events with an outcome of death compared to 5 (4.4%) in the 500-mg/day group. 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 on Day 11 in a centrally cavitating lesion) that led to death that was considered possibly related to IRESSA by the investigator. This patient's death was also reported as cancer related.

Table 19 Number of deaths during or 30 days post treatment in Trial 0039

Category	Number (%) of patients	
	250 mg (N = 102)	**500 mg (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] Patients may fall into more than 1 category. Includes 9 patients who also had an adverse event with an outcome of death.

5.4.4 Adverse events that led to withdrawal

The incidence of withdrawals from IRESSA 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 only drug-related adverse events that led to withdrawal in more than 1 patient were diarrhea, acne, and rash (2 patients each).

Identification of all drug-related adverse events that led to withdrawal is presented in Table 20.

Table 20 Identification of all drug-related adverse events that led to withdrawal in Trial 0039

Dose group	Adverse event	CTC Grade	Outcome	Days on treatment
250-mg/day group				
	Asthenia	4	Ongoing	140[a]
500-mg/day group				
	Acne	3	Recovered	71
	Rash	3	Ongoing	
	Acne	3	Ongoing	92
	Diarrhea	1	Ongoing	63
	Lung hemorrhage	4	Died	11[b]
	Abdominal pain	1	Recovered	14
	Headache		Recovered	
	Diarrhea	1	Recovered	
	Epistaxis	1	Recovered	
	Pruritis	1	Recovered	
	Rash	2	Recovered	
		2	Recovered	

[a] Reported term progressive neurologic deterioration in a patient with CNS metastases who received cranial irradiation just prior to the start of IRESSA.. Onset of the event occurred on Day 85; the event subsequently led to withdrawal after the data cutoff date. 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.
CTC Common toxicity criteria.

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).

5.4.5 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.

5.5 Evaluation of adverse events in Trial 0016

5.5.1 Overview of adverse events

An overview of adverse events occurring in Trial 0016 is presented in Table 21. Nearly all patients (99.0%) in Trial 0016 had at least 1 adverse event. Adverse events are reported by the dose of IRESSA assigned at trial entry.

Table 21 Overview of adverse events in Trial 0016

Category[a]	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	1[b] (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)

[a] Categories are not mutually exclusive; patients may have adverse events in more than 1 category.
[b] The investigator felt unable to assign causality. On review of this case, an AstraZeneca physician assigned a causality of drug-related.
CTC Common Toxicity Criteria.

5.5.2 Adverse events

Those adverse events with an incidence of ≥10% in either dose group are presented in Table 22.

The most frequent adverse events experienced by ≥25% of patients receiving IRESSA 250 mg/day were diarrhea (48.5%), rash (47.6%), pruritus (31.1%), dry skin (29.1%), and asthenia (25.2%). Many adverse events (particularly those associated with the skin and GI

tract) occurred less frequently in patients receiving IRESSA 250 mg/day than in patients receiving 500 mg/day.

Many of the adverse events listed in Table 22, such as asthenia, dyspnea, increased cough, and pain, are consistent with advanced lung cancer.

Table 22 Adverse events with an incidence of ≥10% in Trial 0016

Adverse event (COSTART term) [a]	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)
Hematuria	7 (6.8)	11 (10.4)
Epistaxis	5 (4.9)	19 (17.9)

[a] A patient may have had more than 1 adverse event.
ALT/SGPT Alanine aminotransferase/serum glutamic pyruvic transaminase.
AST/SGOT Aspartate aminotransferase/serum glutamic oxaloacetic transaminase.
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

5.5.2.1 Drug-related adverse events

Drug-related adverse events with an incidence of ≥5% in either dose group are presented in Table 23.

The most frequent drug-related adverse events experienced by ≥10% of patients receiving IRESSA 250 mg/day were rash (46.6%), diarrhea (39.8%), pruritus (30.1%), dry skin (27.2%), nausea (12.6%), increased ALT/SGPT (12.6%), acne (12.6%), and increased AST/SGOT (10.7%). The incidence of all of these events was lower at the 250-mg/day dose than at the 500-mg/day dose.

The majority of patients receiving IRESSA 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 IRESSA did not appear to change with chronic dosing (up to a maximum of nearly 8 months of treatment).

Table 23 Drug-related adverse events with an incidence of ≥5% in Trial 0016

Drug-related adverse event (COSTART term) [a]	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)
Hematuria	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] A patient may have had more than 1 adverse event.
ALT/SGPT Alanine aminotransferase/serum glutamic pyruvic transaminase.
AST/SGOT Aspartate aminotransferase/serum glutamic oxaloacetic transaminase.
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

5.5.2.2 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%) reported 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 and rash were the only drug-related adverse events of CTC Grade 3 or 4 severity with an incidence ≥5% in either dose group (Table 24 and Table 25).

Table 24 Drug-related adverse events of ≥5% by CTC Grade in the 250 mg/day dose group, Trial 0016

Adverse event (COSTART term)[a]	Number (%) of patients[a] (N = 103)				
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Rash	48 (46.6)	27 (26.2)	20 (19.4)	1 (1.0)	0
Diarrhea	41 (39.8)	33 (32.0)	8 (7.8)	0	0
Pruritus	31 (30.1)	26 (25.2)	5 (4.9)	0	0
Dry skin	28 (27.2)	25 (24.3)	3 (2.9)	0	0
Acne	13 (12.6)	10 (9.7)	3 (2.9)	0	0
Nausea	13 (12.6)	11 (10.7)	1 (1.0)	1 (1.0)	0
SGPT increased	13 (12.6)	10 (9.7)	1 (1.0)	2 (1.9)	0
SGOT increased	11 (10.7)	9 (8.7)	2 (1.9)	0	0
Pain	10 (9.7)	9 (8.7)	1 (1.0)	0	0
Anorexia	9 (8.7)	8 (7.8)	1 (1.0)	0	0
Asthenia	8 (7.8)	7 (6.8)	1 (1.0)	0	0
Stomatitis	8 (7.8)	7 (6.8)	1 (1.0)	0	0
Exfoliative dermatitis	8 (7.8)	7 (6.8)	1 (1.0)	0	0
Vomiting	6 (5.8)	4 (3.9)	2 (1.9)	0	0
Seborrhea	6 (5.8)	1 (1.0)	4 (3.9)	1 (1.0)	0
Hematuria	6 (5.8)	5 (4.9)	1 (1.0)	0	0

[a] A patient may have had more than 1 adverse event.
ALT/SGPT Alanine aminotransferase/serum glutamic pyruvic transaminase.
AST/SGOT Aspartate aminotransferase/serum glutamic oxaloacetic transaminase.
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.
CTC Common Toxicity Criteria.

Table 25 Drug-related adverse events of ≥5% by CTC Grade in the 500 mg/day dose group, Trial 0016

Adverse event (COSTART term)	Number (%) of patients[a] (N = 106)				
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Rash	73 (68.9)	31 (29.2)	35 (33.0)	6 (5.7)	1 (0.9)
Diarrhea	61 (57.5)	36 (34.0)	18 (17.0)	7 (6.6)	0
Pruritus	38 (35.8)	34 (32.1)	3 (2.8)	1 (0.9)	0
Dry skin	31 (29.2)	23 (21.7)	8 (7.5)	0	0
Nausea	25 (23.6)	17 (16.0)	7 (6.6)	1 (0.9)	0
SGOT increased	24 (22.6)	15 (14.2)	6 (5.7)	2 (1.9)	1 (0.9)
SGPT increased	25 (23.6)	14 (13.2)	5 (4.7)	5 (4.7)	1 (0.9)
Vomiting	21 (19.8)	14 (13.2)	7 (6.6)	0	0
Anorexia	20 (18.9)	11 (10.4)	8 (7.5)	1 (0.9)	0
Pain	17 (16.0)	15 (14.2)	2 (1.9)	0	0
Acne	15 (14.2)	5 (4.7)	8 (7.5)	2 (1.9)	0
Epistaxis	12 (11.3)	11 (10.4)	1 (0.9)	0	0
Asthenia	11 (10.4)	7 (6.6)	3 (2.8)	1 (0.9)	0
Conjunctivitis	10 (9.4)	8 (7.5)	2 (1.9)	0	0
Stomatitis	8 (7.5)	8 (7.5)	0	0	0
Exfoliative dermatitis	9 (8.5)	5 (4.7)	2 (1.9)	2 (1.9)	0
Nail disorder	9 (8.5)	3 (2.8)	5 (4.7)	1 (0.9)	0
Abdominal pain	8 (7.5)	6 (5.7)	2 (1.9)	0	0
Weight loss	6 (5.7)	4 (3.8)	2 (1.9)	0	0
Blepharitis	6 (5.7)	3 (2.8)	3 (2.8)	0	0

[a] A patient may have had more than 1 adverse event.
ALT/SGPT Alanine aminotransferase/serum glutamic pyruvic transaminase.
AST/SGOT Aspartate aminotransferase/serum glutamic oxaloacetic transaminase.
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.
CTC Common Toxicity Criteria.

5.5.3 Deaths

The number (%) of patients who died during Trial 0016, and the primary causes of death (disease progression or adverse event), are summarized in Table 26.

Twenty-three (22.3%) patients in the 250-mg/day group died during treatment or posttreatment (ie, within 30 days after the last dose of IRESSA) 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 500-mg/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 was unable to assign causality. On review of this case, this death was deemed to be drug-related. This patient was a 62-year-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 (COSTART term: pneumonia) and died 2 days after onset. The adverse event was CTC Grade 4.

Table 26 Number of deaths during or 30 days post treatment in Trial 0016

Category	Number (%) of patients	
	250 mg (N = 103)	**500 mg (N = 106)**
Patients who died	23 (22.3)	12 (11.3)
Patients whose death was considered cancer related[a]	22 (21.4)	11 (10.4)
Patients who had an adverse event that resulted in death	4 (3.9)	1 (0.9)

[a] Patients may fall into more than 1 category.

5.5.4 Adverse events that led to withdrawal

The incidence of withdrawals from IRESSA 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 only drug-related adverse events that led to withdrawal of more than 1 patient were rash, pneumonia, increased ALT/SGPT, and increased AST/SGOT.

Identification of drug-related adverse events that led to withdawal is provided in Table 27.

Table 27 Identification of drug-related adverse events that led to withdrawal in Trial 0016

Dose group	Adverse event	CTC Grade	Outcome	Days on treatment
250-mg/day group				
	Bundle branch block	3	Ongoing	112
	ALT/SGPT increased	3	Resolved	41
500-mg/day group				
	Pneumonia	4	Died	59
	Diarrhea	3	Ongoing	2
	Nausea	3	Resolved	2
	Vomiting	2	Ongoing	2
	Rash	1	Ongoing	10
	Liver function tests abnormal	3	Ongoing	57
	Pneumonia	3	Ongoing	87
	Hypoxia	3	Resolved	88
	Generalized edema	2	Ongoing	24
	Hypoproteinemia	3	Ongoing	57
	ALT/SGPT increased	4	Resolved	29
	AST/SGOT increased	4	Resolved	29
	Deep thrombophlebitis	4	Ongoing	92
	ALT/SGPT increased	3	Ongoing	29
	AST/SGOT increased	3	Ongoing	43
	Rash	3	Resolved	7

ALT/SGPT Alanine aminotransferase/serum glutamic pyruvic transaminase.
AST/SGOT Asparate aminotransferase/serum glutamic oxaloacetic transaminase.
CTC Common toxicity criteria

5.5.5 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. Diarrhea, anemia, and pneumonia were the only drug-related serious adverse events experienced by more than 1 patient (3, 2, and 3 patients, respectively).

5.6 Clinical laboratory values and vital signs

Clinical laboratory values were variable in this population of advanced cancer patients. Many patients had laboratory values that were outside the normal range at trial entry, reflecting their clinical status. The key findings from the review of the clinical laboratory parameters in the Phase I and II trials were:

- A small number of significant, asymptomatic increases in liver transaminases have been observed at the 250-mg/day dose and with a slightly higher incidence at the 500-mg dose. Many of these patients had pre-existing liver metastases. Patients with pre-existing hepatic dysfunction did not appear to be at increased risk for these changes.

- Asymptomatic hematuria has been observed, but the clinical significance of this is unclear. There do not appear to have been any sequelae to these observations, in particular no reports or observations of impaired renal function.

- No clinically significant changes in hematological or renal parameters were observed.

5.7 Adverse events in special populations

Assessment of the adverse event profile of IRESSA in special populations does not raise safety concerns based on gender, ethnic origin, age, body mass index, or performance status. IRESSA was well tolerated in all patient populations assessed, and no dosage adjustment is considered necessary in any of them.

Assessment of the adverse event profile of IRESSA in patients with mild to moderate renal impairment did not raise safety concerns regarding the use of IRESSA in these patient populations. Only 5 patients in the Phase II trials had hepatic impairment at trial entry (patients with liver metastases at trial entry were allowed into the study if their SPGT/SGOT hepatic enzymes were ≤5X the upper limit of the reference range), and consequently, no conclusions could be drawn about the use of IRESSA in this patient population.

In Japanese vs non-Japanese and white vs non-white populations, adverse events were comparable. However, Grade 1 or 2 skin adverse events were reported at higher incidences in Japanese patients than in non-Japanese patients.

Hepatic enzyme elevations were reported more frequently as adverse events by the Investigators in Japanese patients in Trial 16; however, they did not reflect the smaller percentage of patients who had >1 Grade worsening of actual laboratory values recorded concurrently. In Trial 39, a small incidence of reported hepatic enzyme elevation adverse events mirrored the percentage of patients with hepatic laboratory abnormalities.

Assessment of the adverse event profile of IRESSA in patients receiving concomitant medications did not raise any additional safety concerns regarding IRESSA when co-administered with other drugs. International Normalized Ratio (INR) elevations and/or

bleeding events have been reported in some patients taking warfarin in the EAP, and consequently, patients receiving warfarin concomitantly with IRESSA should be monitored regularly for changes in P-T or INR.

5.8 Adverse events of special interest conclusions

- Skin and gastrointestinal events were the most commonly reported adverse events. The majority of these were mild (CTC Grade 1), and at the 250-mg/day dose, did not lead to any patients withdrawing from treatment.

- In patients receiving IRESSA 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.

- There were no clear trends observed in ECGs or PR intervals for patients during trial treatment. Consequently, there is no requirement for routine monitoring of cardiac function for patients receiving IRESSA.

5.9 4-month safety update conclusions

Patients' exposure to IRESSA in Trials 0039 and 0016 has increased since the data cutoff dates used for the ISS (1 August 2001 and 22 May 2001, respectively), with an additional 57 patients from the completed IRESSA Phase II trials (pivotal Trial 0039 and supporting Trial 0016) having been exposed to IRESSA for >6 months data cutoff date of 1 March 2002. This additional adverse event data from these 2 trials is remarkable for both the paucity of any drug-related adverse events and the lack of new, unusual, or cumulative toxicity. As previously observed, the incidence of drug-related adverse events in both trials was lower in patients who received IRESSA 250 mg/day compared to those who received 500 mg/day.

In addition, serious adverse event data from over 8000 patients enrolled on the Expanded Access or compassionate use program was included. This data was also remarkable for relative paucity of serious adverse events. A large number of these events were those associated with disease progression. Within the group of drug-related SAEs reported, the only new findings included 2 patients with a severe type of immune-mediated skin toxicity and a possible warfarin interaction in a small number of patients.

The net result of this additional safety information is that the safety profile of IRESSA continued to be consistent with the safety data presented in the ISS.

The extended follow-up of patients on the 2 Phase II trials and these findings are particularly of note in a patient population with recurrent, refractory, and advanced cancer when viewed in the context of the safety and adverse event profiles with either BSC or single agent chemotherapy as outlined in Section 2.2.

5.10 Overall safety conclusions

Reflecting the highly specific and molecularly targeted inhibition of the EGFR tyrosine kinase pathways, the safety profile of IRESSA was predictable, consistent pre-clinically and clinically, and to variable degrees involved only epithelially derived, EGFR dependent tissues. The most frequent effects were gastrointestinal or skin-related. The types and frequency of gastrointestinal (GI) side effects are those familiar to both oncologists and cancer patients – diarrhea occurring in one-half or more of patients and nausea and vomiting in about one-quarter. However, the severity of these GI side effects with IRESSA was much less as these were predominantly Grade 1 or 2 events. As a result, prophylactic medications were not used and only routine over the counter anti-diarrheal medications were needed for management in the great majority of patients.

Effects on the skin included a characteristic acne-like or erythematous rash predominantly in the facial area distinct from rashes typically seen with different chemotherapy agents. Again the severity of this rash was largely Grade 1, occasionally Grade 2 and was primarily manageable with topical lotions or creams. Rash did not worsen over time. As in preclinical studies, corneal epithelium changes were uncommon.

Data from nonclinical studies suggest that IRESSA may have the potential to cause prolongation of the ECG PR or QT 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. However, while significant cardiac events did occur, they were infrequent and occurred only in patients with prior cardiac history. None of the cardiac events were suggestive of QT prolongation or related arrhythmias.

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

There were no significant differences in adverse events comparing Japanese patients to non-Japanese patients with the exception of mild, minor skin changes. There was an apparent higher frequency of hepatic transaminase elevation in Trial 0016 patients but this reflects differences in reporting rather than actual differences since comparison of actual biochemical results does not differ.

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 IRESSA.

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

INR elevations and/or minor bleeding events have been reported in some patients taking warfarin in the EAP while on IRESSA therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time and INR.

Overall, the incidence of drug-related adverse events, rate of dosage reduction, interruptions, or withdrawal of therapy due to adverse events was lower in patients who received IRESSA 250-mg/day compared to those who received 500-mg/day. This experience was less with either IRESSA dose, or especially the 250-mg dose, than the experience with single agent chemotherapy. Largely due to the lack of marrow suppression, infections were either minor or likely disease related pneumonia.

In sum, especially at the recommended 250-mg dose, IRESSA is a drug with a modest and very tolerable side effect profile in the palliative setting of patients already compromised by advanced cancer, sequelae of previous chemotherapy and radiotherapy, and other illnesses.

6 CONCLUSIONS

After a patient with NSCLC has received both a platinum-based regimen and docetaxel, there are no available standard chemotherapy agents or regimens with proven benefit. Such patients thus lack a therapy option while experiencing disease-related symptoms due to direct and indirect effects of advanced cancer in general and obstructive or destructive tumor in the lung in particular. Biologically-based, molecularly targeted therapies offer the potential of therapeutic benefit coupled with limited and predictable side effects. One of the first of a new class of agents, IRESSA specifically targets and inhibits the EGFR-TK, which in turn inhibits or blocks biochemical reactions controlling the survival and proliferation of malignant, epithelially derived tumors such as non-small cell lung cancer.

New agents, which provide meaningful, durable tumor regression and disease control with accompanying disease-related symptom relief and improved overall quality of life, are needed for patients whose expected survival measured in weeks to months.

Phase I trials, which included 100 NSCLC patients, showed that the safety profile was modest and confined to the gastrointestinal tract and skin. Patients with NSCLC appeared to benefit significantly with rapid but durable tumor response; rapid symptom relief was also noted. In both the pivotal Trial 0039 and supportive Trial 0016, with a total of over 400 patients with recurrent NSCLC, durable objective responses occurred in 8.8% to 19.0% of patients and approximately 40% of patients had improvement of disease related symptoms for at least one month associated with quality of life improvement. Of clinical relevance and significance include rapidity of response, reduction of bulky or large tumor burden with responses occurring across the entire patient spectrum, irrespective of demographic, baseline clinical status, prior treatment history, and disease characteristics.

The high degree of association of radiographic response (and disease stabilization) with disease-related symptom improvement is mutually supportive and provides complementary information concerning patient benefit. To the patient receiving palliative care, a radiographic

response is meaningless unless it is relatively durable and accompanied by a benefit or improvement directly experienced by the patient. To the clinician having to make care and management decisions in the palliative setting, radiographic evidence of tumor reduction or control is a key element in assessing the value of the therapy. Lastly, both patient and physician need an agent, which is safe and tolerable so as not to further compromise an already comprised state. The safety profile and tolerability of IRESSA, particularly at the recommended lower 250-mg dose, are very acceptable for the great majority of patients, even in the palliative setting with clinically compromised patients.

Overall, IRESSA has demonstrated comparable efficacy and safety findings in 2 randomized clinical trials. Almost one-half of patients experienced significant and relevant clinical benefit with objective radiographic response and/or improvement in disease-related symptoms. One-third of patients judged their quality of life to be improved. A low frequency of drug-related significant, non-life threatening side effects or therapy withdrawals due to side effects occurred at the recommended 250-mg dose.

IRESSA has demonstrated an excellent therapeutic index in the palliative setting for previously treated patients with NSCLC.

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APPENDIX A PRESCRIBING IMPLICATIONS

- As asymptomatic increases in liver transaminases have been observed, periodic liver function testing is recommended. IRESSA should be used cautiously in the presence of mild-to-moderate increases of liver transaminases. Discontinuation should be considered if changes are severe.

- Substances that are inducers of CYP3A4 activity may increase metabolism and decrease IRESSA concentrations. Therefore, comedication with CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampicin, barbiturates, or St. John's Wort) may potentially reduce efficacy. Substances that are potent inhibitors of CYP3A4 activity may decrease metabolism and increase IRESSA plasma concentrations. This increase may be clinically relevant as adverse experiences are related to dose and exposure. Drugs that cause significant sustained elevation in gastric pH may reduce plasma concentrations of IRESSA and therefore potentially may reduce efficacy.

- In the event of developing any eye symptom or diarrhea, patients should be advised to seek medical advice promptly.

- Patients receiving warfarin should be monitored regularly for changes in prothrombin time or INR.

- IRESSA should not be given to pregnant or lactating women.

- Dose adjustments are not required for elderly patients as no differences in safety or efficacy were observed between younger and older patients.

- There is a low potential for abuse and overdosage with IRESSA.