

2 STUDY SYNOPSIS

Name of Company: OSI Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Tarceva™ (OSI-774)	Volume:	
Name of Active Ingredient: Erlotinib hydrochloride (USAN) erlotinib (INN)	Page:	
Title of Study: BR.21. A Randomized Placebo-Controlled Study of OSI-774 (Tarceva™) in Patients With Incurable Stage IIIB/IV Non-Small Cell Lung Cancer Who Have Failed Standard Therapy For Advanced or Metastatic Disease		
Investigators and Study Centers: In this multicenter study, 731 patients were randomized across 86 centers in 17 countries. A complete list of Investigators and centers is provided in Appendix 16.1.4 .		
Publication (reference) Appendix 16.1.11: Shepherd FA, Pereira J, Ciuleanu TE, Tan EH, Hirsh V, Thongprasert S et al. A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure of 1 st line or 2 nd line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial. Proc Am Soc Clin Oncol 2004; [Abstract 7022].		
Studied Period: Date first patient randomized: 01 NOV 2001 Date last patient randomized: 31 JAN 2003 Data field cut-off date: 30 JAN 2004 Date of Database Lock: 23 APR 2004	Phase of Development: III	
Objectives: In patients with incurable Stage IIIB/IV non-small cell lung cancer (NSCLC) who have failed 1 or 2 standard therapies for advanced or metastatic disease, the objectives were: <u>Primary:</u> To compare overall survival between the 2 treatment arms. <u>Secondary:</u> To compare the 2 treatment arms for: <ul style="list-style-type: none"> • Quality of Life (QoL) as measured by the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the lung cancer module QLQ-LC13; • progression-free survival (PFS); • response rates (RR); • response duration; • nature, severity, and frequency of toxicities; and: <ul style="list-style-type: none"> • to correlate the expression of tissue epidermal growth factor receptor (EGFR) levels (at diagnosis) with outcomes and response to treatment; • to measure and correlate trough levels of OSI-774 with clinical responses and/or adverse events. 		

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<p>Methodology:</p> <p>This was a randomized, double-blind, placebo-controlled study of erlotinib conducted in 731 patients with NSCLC who had failed at least 1 but no more than 2 prior regimens. Patients were stratified at enrollment by center, number of prior regimens, prior platinum therapy, best response to prior therapy, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) and randomized 2:1 to receive erlotinib 150 mg tablets orally or placebo. Treatment could continue daily until disease progression or unacceptable toxicity.</p> <p>Efficacy was evaluated by periodic assessments of survival and effect on symptoms reported by patients on the EORTC QLQ-C30 and QLQ LC-13 quality of life questionnaires. Serial measurements of all disease sites were performed every 8 weeks and response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST).</p> <p>Safety was assessed every 4 weeks by, monitoring the incidence, severity, and relationship of AEs to study drug and by evaluating hematology, biochemistry and changes in physical examination. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (NCI CTC) criteria, version 2.0. Patients were assessed 4 weeks after discontinuing protocol treatment and then followed every 12 weeks until death. Vital signs were not collected in this study.</p>		
<p>Number of Patients (planned/analyzed):</p> <p>The planned sample size of 700 patients was selected in order to have 90% power to demonstrate a 33% survival benefit in the erlotinib arm (two-sided $\alpha = 0.05$). A total of 582 deaths needed to be observed to perform the analysis. Patients were randomized in a 2:1 ratio to receive either erlotinib or placebo. A total of 731 patients were randomized and all are included in the survival analysis.</p>		
<p>Diagnosis and Main Criteria for Inclusion:</p> <p>Patients who were at least 18 years of age and had given written consent were eligible for the study if they had a histologically or cytologically confirmed diagnosis of incurable Stage IIIB/IV NSCLC, had received at least 1 but no more than 2 prior regimens of which at least 1 had to be combination chemotherapy (if < 70 years old) or had up to 2 prior single-agent regimens (if ≥ 70 years old), had an ECOG PS of 0 to 3, had adequate renal and hepatic functions defined by protocol criteria, and had recovered from the toxic effects of prior therapies. Further, an eligible patient had to have completed a baseline QoL questionnaire and had to be willing to complete additional forms during the study, had not received prior treatment with any epidermal growth factor receptor (EGFR) inhibitor, did not have other serious medical conditions, and was not pregnant or lactating (for women of child-bearing potential).</p>		
<p>Test Product, Dose and Mode of Administration, Batch Numbers:</p> <p>Erlotinib was formulated as round, white, unscored, film-coated tablets in 25 mg, 100 mg, and 150 mg strengths. They were supplied in 60-cc blue-white high density polyethylene (HDPE) bottles with a screw-off cap bearing white, printed, 2-panel labels. Patients took a dose of 150 mg orally once a day in the morning with up to 200 mL of water, at least 1 hour before or 2 hours after ingesting any food or other medications. Study drug could be withheld or reduced for toxicity. Dose escalation was not permitted.</p> <p>Lot numbers: 25 mg (██████████); 100 mg (██████████); 150 mg (██████████)</p>		

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Placebo, Dose and Mode of Administration, Batch Numbers: Placebo tablets were matched to erlotinib in color, shape, size, and packaging. The “dose” of 150 mg was taken orally once a day in the same manner and timing as for erlotinib. Lot numbers: 25 mg (), 100 mg (); 150 mg ()		
Duration of Treatment: Patients began treatment within 2 days of randomization and continued daily therapy until disease progression was documented or until they experienced unacceptable toxicity.		
Criteria for Evaluation: <u>Efficacy:</u> All 731 randomized patients were included in the analysis of the primary endpoint, overall survival (intent-to-treat analysis). Patients were followed for survival status every 4 weeks during the study and every 12 weeks post-treatment until death. All patients who completed at least the baseline and one subsequent set of QoL forms were evaluable for the QoL analysis. Patients who had at least 1 measurable lesion and at least 1 tumor assessment after baseline were evaluable for response, unless early progression was documented, in which case they were also considered evaluable. <u>Safety:</u> Patients who received at least 1 dose of study medication were included in the safety analysis (n = 728). <u>PK:</u> For exploratory erlotinib exposure-effects analysis, median erlotinib exposure was evaluated in erlotinib treated patients with ≥ 3 independent plasma samples drawn predose following 5 consecutive days of dosing at 150 mg.		
Statistical Methods: All randomized patients were included in intent-to-treat analysis of overall survival. In the primary analysis, the 2 treatment arms were compared using the Log Rank test stratified for ECOG performance status at randomization (0+1 vs 2+3), best response to prior therapy at randomization (CR or PR vs SD vs PD), number of prior regimens at randomization (1 vs 2), exposure to prior platinum at randomization (prior platinum vs no prior platinum), EGFR expression status (positive vs negative vs unknown). The effects of other potential prognostic factors on overall survival were assessed using Cox regression analysis. Unstratified Kaplan-Meier survival curves were generated and 95% confidence intervals for the median survival in each treatment arm were calculated. The primary endpoints in the QoL analysis were the time from randomization to deterioration in the following three QoL symptoms: cough, dyspnea, and pain. Patients were considered to have deteriorated for a given symptom if their change score from the baseline on the domain/single item defining this symptom was 10 points or higher at any time-point after the baseline assessment. For each symptom, all patients who had a baseline and at least 1 of the follow-up QoL assessments were included in the time to deterioration analysis. Patients were censored at the time of the last QoL questionnaire completion if they had not deteriorated before. The time to deterioration in each symptom was compared between the 2 treatment arms using unstratified Log Rank tests, and the Hochberg procedure was used to adjust the p-values of the Log Rank tests for these 3 symptoms.		

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Response rate, duration of response and progression-free survival were medically verified in detail by the NCIC CTG and OSI for the first 330 randomized patients. In addition, for patients in this group considered having a CR or PR, or for borderline evaluations of SD versus PR, central review of imaging documentation was performed on an ongoing basis by an independent radiologist in ██████████, Canada. Differences in assessment between the Investigator/NCIC CTG ██████████ and the independent radiologist were reconciled before closing the database. For the remaining 401 patients, the Investigators' assessment was reconciled with the assessment of the NCIC CTG ██████████.

Tables and listings in this Clinical Study Report may display rounded values, however, the computation results in all text/tables are based on full number precision stored in the clinical database.

Summary and Conclusions:

Patient Characteristics:

A total of 731 patients were randomized in the study, 488 patients in the erlotinib arm and 243 patients in the placebo arm. Demographic characteristics were well balanced between the 2 treatment arms. About two-thirds of the patients were male, and about one-third were 65 years or older. The median age in the erlotinib group was 62 years and in the placebo group 59 years. The majority of patients were White (78% and 77%) or Oriental (13% and 12%). The baseline ECOG PS was 0 – 1 in 65% and 68%, and 2 – 3 in 35% and 32%. About one-fifth of the patients never smoked (21% and 17%).

In addition to all patients having received prior chemotherapy, 54% in the erlotinib arm and 59% in the placebo arm had received radiotherapy. The number of prior chemotherapy regimens was similar between the 2 treatment arms: approximately half of the patients had received 1 prior regimen and the other half 2 prior regimens. One percent of the patients had received a third chemotherapy regimen. Most patients had received prior platinum (93% and 92%, respectively), and 36% and 37% of patients had received a prior taxane.

Disease characteristics were well balanced between the 2 treatment arms. Adenocarcinoma was reported in 50% of patients in the erlotinib arm and 49% in the placebo arm and squamous cell carcinoma in 30% and 32%, respectively. The majority of patients had Stage IIIB or IV at diagnosis (83% and 79%, respectively). The median time from initial diagnosis to randomization was 13.1 months in the erlotinib arm versus 12.2 months in the placebo arm.

Pathology blocks or slides were available and results were interpretable for 31% of the patients in the erlotinib arm and for 35% of the patients in the placebo arm. It is unknown how many of the available samples are from the time of initial diagnosis or at a subsequent relapse. For these patients, the distribution of the receptor status was balanced between the 2 treatment arms. A positive EGFR expression was defined as having at least 10% of cells staining for EGFR. In the erlotinib arm, 16% of patients had a positive EGFR expression and 15% had a negative status, compared with 20% and 15% in the placebo arm. In the erlotinib arm, 6% of patients had a staining in ≥ 75% of cells compared with 5% in the placebo arm.

In summary, this was a population of patients with advanced/metastatic NSCLC, who had failed 1 or 2 prior regimens of chemotherapy and who were deemed no longer candidates to receive further cytotoxic therapy.

Summary of Efficacy:

The Statistical Analysis Plan (SAP) specified that analyses would be performed after 582 deaths had been observed. On the field cut-off date, 587 deaths had occurred and 144 patients were still alive: 110 patients (23%) in the erlotinib arm and 34 patients (14%) in the placebo arm. Only 7 patients were declared lost to

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follow-up and they had been followed for 0.4 to 11.1 months. The remainder of patients who were still alive at the field cut-off date had been followed for 12.0 to 25.9+ months, and all patients but 1 had their last contact date at the end of January 2004.

A total of 28 patients were still taking study drug at the time of the field cut-off date (27 in the erlotinib arm and 1 in the placebo arm).

This study demonstrated a statistically significant and clinically meaningful prolongation of survival in patients treated with erlotinib compared with placebo: the HR for death in the erlotinib arm relative to the placebo arm estimated from the primary analysis (adjusted for stratification factors at randomization and EGFR expression status) was 0.73 (95% CI, 0.60 – 0.87) (p = 0.001), indicating that erlotinib reduced the risk of death by 27% compared with placebo. The median survival was 6.67 months in the erlotinib arm compared with 4.70 months in the placebo arm, a 42% improvement. The actuarial 12-month survival rates were 31.2% and 21.5%, respectively, for the erlotinib and placebo arms.

In an exploratory multivariate survival analysis that included additional pretreatment factors, the effect of erlotinib remained statistically significant, with an adjusted HR of 0.73 that was exactly the same as the adjusted HR produced from the primary analysis. Other factors that were significantly associated with survival included performance status, best response to prior therapy, exposure to prior platinum, smoking status, histology, weight loss in the previous 6 months, and time from initial diagnosis to randomization. Factors that were not associated with survival in this multivariate analysis included number of prior regimens, exposure to prior taxanes, geographic location, EGFR status (including the interaction between EGFR expression and treatment), gender and age.

In a subset analysis of factors examined in exploratory univariate analyses (the stratification factors at baseline, EGFR status, prior exposure to taxanes, smoking history, gender, age, histology, prior weight loss, time between initial diagnosis and randomization, and geographic location), nearly all of the HRs in the erlotinib arm relative to the placebo arm were less than 1.0, and most were in the vicinity of 0.76, the HR of the univariate treatment effect. No subsets were identified where the HR was significantly greater than 1.

Significantly more patients in the placebo arm (42%) received subsequent therapy (chemotherapy, radiotherapy and/or EGFR inhibitors) compared with the erlotinib arm (33%) (p = 0.033). After censoring for subsequent therapy, the survival in the erlotinib arm remained significantly better than in the placebo arm (median survival 7.8 months versus 5.0 months, respectively, p = 0.029).

The main endpoints in the quality of life/symptom benefit analysis were time to deterioration of the following 3 QoL symptoms: cough, dyspnea, and pain, 3 of the more prevalent and specific lung cancer symptoms. Baseline scores for each of the 3 symptoms were available for the majority of patients and were well balanced between treatment arms. A total of 63% of the patients in the erlotinib arm and 64% of the patients in the placebo arm had at least a baseline and one follow-up score for cough, and 74% and 75% of the patients, respectively, each for dyspnea and pain. A total of 461 patients were included in the analysis of cough, 542 patients in the analysis of dyspnea and 545 patients in the analysis of pain. The median time to deterioration of cough was 28.1 weeks in the erlotinib arm and 15.7 weeks in the placebo arm, p = 0.041, HR 0.75 (95% CI, 0.56 – 1.00). For dyspnea, it was 20.4 weeks in the erlotinib arm and 12.1 weeks in the placebo arm, p = 0.031, HR 0.72 (95% CI, 0.56 – 0.93) and for pain it was 12.1 weeks in the erlotinib arm and 8.1 weeks with placebo p = 0.040, HR 0.77 (95% CI, 0.61 – 0.97).

These symptom benefits could not be attributed to use of radiotherapy or concomitant medications.

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The best response was assessed in patients with measurable disease (427 patients in the erlotinib arm and 211 patients in the placebo arm). Two responses were observed in the placebo arm (1 CR and 1 PR) for a 0.9% response rate (95% CI, 0.1 – 3.4%). Both responses were in the group of patients who were less intensely medically reviewed. A total of 4 CRs and 34 PRs were observed among the patients with measurable disease treated with erlotinib, for an objective response rate of 8.9% (95% CI, 6.4 – 12.0%). An additional patient with only nonmeasurable lesions at baseline also achieved a CR while treated with erlotinib.

Stable disease was observed in 35.1% of erlotinib-treated patients with measurable disease, compared with 26.5% of placebo-treated patients, for a CR + PR + SD rate of 44.0% and 27.5%, respectively. This difference was statistically significant, p = 0.004. The responses obtained with erlotinib were durable: for patients with measurable disease, the median response duration was 34.3 weeks, ranging from 9.7 to 57.6+ weeks.

An exploratory survival analysis, excluding responding patients and patients who were inevaluable for response, showed that the median survival of the erlotinib-treated patients was 7.4 months, compared with a median of 6.7 months in the placebo arm, HR = 0.82, p = 0.037.

The median PFS was 9.71 weeks in the erlotinib arm (95% CI, 8.43 – 12.43 weeks) compared with 8.00 weeks in the placebo arm (95% CI, 7.86 to 8.14 weeks). This difference was statistically significant (Log Rank p-value < 0.001). The actuarial 26-week (6-month) PFS rates were 24.5% and 9.3%, respectively, for the erlotinib and placebo arms. The hazard ratio (HR) for progression in the erlotinib arm relative to the placebo arm, estimated from a univariate Cox model, was 0.64 (95% CI, 0.54 – 0.75).

In summary, erlotinib therapy provided a statistically significant and clinically meaningful prolongation of survival and progression free survival in patients with incurable NSCLC having failed at least 1 prior chemotherapy regimen. Importantly, additional patient benefit was demonstrated with longer time to deterioration of lung cancer symptoms (cough, dyspnea and pain), not driven by an increased use of palliative concomitant medications or radiation. In addition, durable tumor responses and prolonged disease stabilization were achieved.

Summary of Safety:

Overall, erlotinib 150 mg daily was well tolerated by most patients. Dose reduction to 100 mg occurred in 15% of erlotinib-treated patients and further reduction to 50 mg in 4% of patients, compared with 1% and < 1% in placebo-treated patients. Discontinuation due to protocol toxicity occurred in 5% in the erlotinib arm and 2% in the placebo arm.

The overall incidence of AEs regardless of causality was similar between the treatment arms (99% vs 96%). Severe events (NCI CTC Grade 3 or 4) occurred in 62% in the erlotinib arm compared with 58% in the placebo arm. AEs considered treatment-related occurred in 85% in the erlotinib arm and 51% in the placebo arm.

Rash (75% vs 17%) and diarrhea (54% vs 18%) were the most common AEs regardless of causality. Most were Grade 1 and 2 in severity (rash: 66% vs 17%; diarrhea: 48% vs 17%) and manageable without intervention, however, guidance was provided for the use of appropriate medication in more severe cases. Severe rash and diarrhea occurred in 9% and 6%, respectively, in erlotinib-treated patients and each resulted in study discontinuation in 1%, however, 10% and 4% needed dose reduction for rash and diarrhea, respectively.

Respiratory disorders were frequently reported (66% vs 62%), however, the majority were associated with

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progression of the underlying disease. Special attention was paid to pulmonary toxicities such as possible drug-induced interstitial lung disease (ILD). The protocol was amended early during the study to alert Investigators to monitor for possible signs and symptoms of interstitial pneumonia and to inform patients about the potential risk. Because drug-induced ILD is difficult to diagnose and ultimately requires histological confirmation, potentially relevant MedDRA preferred terms were selected to identify patients for further medical evaluation. When these terms were applied for conditions present at baseline, the incidence of pre-existing ILD-like conditions was 3% of the patients in the erlotinib arm and 5% of patients in the placebo arm, with pulmonary fibrosis accounting for the majority of these events. During the study, 6 patients were classified as having ILD-like SAEs. These included 4 erlotinib-treated patients and 2 placebo-treated patients, which, due to the 2:1 randomization, represent an incidence of 0.8% in each arm. Histological confirmation was possible in 1 erlotinib-treated patient only. One patient in each group died because of the event and the Investigator attributed the death to study drug in both cases before unblinding. More erlotinib-treated patients (7%) experienced pulmonary infections (pneumonia, sponsor-assessed probable pneumonia, lung or respiratory infection, lung abscess) compared with placebo-treated patients (2%). Considering the longer survival time and time on treatment for erlotinib-treated patients, the incidence of infections per patient week was not different between study arms.

More nausea (33% vs 24%) and vomiting (23% vs 19%) were reported in the erlotinib arm. Three patients developed Grade 3 renal insufficiency in the erlotinib arm, compared with none of the placebo-treated patients. Each patient had confounding co-morbidities likely to have caused renal impairment rather than a direct nephrotoxic effect.

There was no apparent hematological toxicity associated with erlotinib therapy. The possibility of an interaction between erlotinib and warfarin required close monitoring of INR in patients receiving such anticoagulants. Patients on warfarin frequently showed INR values outside therapeutic range. INR shifts from baseline to values that are associated with increased risk for bleeding complication (ie, INR ≥ 4) were seen in 26% vs 21% of warfarin-treated patients in the erlotinib and placebo arms, respectively. Whether patients received warfarin or not, reports of clinically recognized bleeding occurred in 24% of erlotinib-treated-patients compared to 17% with placebo, however, most were inconsequential Grade 1 episodes of hemoptysis and epistaxis. Severe bleeding cases include 8 erlotinib-treated patients (2%) with serious gastrointestinal hemorrhage and none in placebo arm. Concurrent warfarin administration was present in 2 of these 8 patients and other medications (ie, NSAID) and ulcer disease contributed as well.

The pharmacological effect of EGFR inhibition is presumably accountable for the observed ophthalmological disorders such as dry eyes and conjunctivitis. Overall, 27% of patients in the erlotinib arm and 9% of patients in the placebo arm experienced eye disorders. Most were mild in severity and none required medical intervention other than the use of topical eye drops.

The effect of erlotinib treatment on liver function was negligible. Few patients developed clinically meaningful changes in liver function tests and most were confounded by the presence of liver metastases. No adverse cardiac effects could be attributed to erlotinib therapy including development of arrhythmia.

In summary, this randomized, placebo-controlled trial has confirmed the favorable safety profile of erlotinib in a population of patients with advanced NSCLC, having failed prior chemotherapy. The most common events were rash and diarrhea, mostly mild or moderate in severity, as expected for this class of agents. The high frequency of AEs including severe events is consistent with what can be expected in a patient population with previously treated, advanced and symptomatic NSCLC. No other safety concerns have emerged from this large safety dataset.

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<p>Summary of Exposure and Pharmacokinetics:</p> <p>The target erlotinib dose in this study was 150 mg and the majority of patients (81%) remained at this dose for the duration of treatment. Only a subset of these patients (n = 133, 27% of erlotinib-treated patients) had sufficient plasma sampling for evaluation (≥ 3 independent samples drawn predose following 5 consecutive days of dosing at 150 mg). Within this group, the median steady state erlotinib trough plasma concentration was 1224 ng/mL, with a range of < 1 ng/mL to 3535 ng/mL.</p> <p>Erlotinib exposure data were compared to patient baseline characteristics. Exposure was similar between males and females. The median OSI-420 plasma concentration was increased by 58.6% (or 46.9 ng/mL) and the sum of erlotinib and OSI-420 was increased by 17% (or 218 ng/mL) in the patients who were ≥ 65 years old, compared to younger patients. Former smokers or patients who had never smoked had median erlotinib and OSI-420 plasma concentrations that were twice that of the patients who were current smokers. No relationship was found between the tumor histology (adenocarcinoma vs other) and erlotinib exposure.</p> <p>Patients in the PK subpopulation had a longer duration of treatment with consistently higher dose intensity. Patients in this group with higher erlotinib plasma exposure did not experience a higher incidence of notable treatment-related adverse events. There were nonsignificant trends towards an increased median exposure to erlotinib in patients with more severe rash and diarrhea. However, the patient subset analyzed was too enriched with the longer surviving patients to assess the impact of erlotinib exposure on survival.</p> <p>In summary, erlotinib plasma exposure could only be evaluated in a subset of better performing patients. This prohibited a meaningful analysis of erlotinib versus survival outcomes. The analysis of erlotinib plasma exposure data from this study, although limited, supports that patient characteristics such as race, gender, previous chemotherapy, and histology did not have an impact on erlotinib exposure. Furthermore, in this subpopulation of patients who had a longer duration of treatment with consistently higher dose intensity, there were no statistically significant correlations between erlotinib exposure and the incidence of adverse events.</p>		
<p>Conclusions:</p> <p>BR.21 is the largest placebo-controlled trial reported to date evaluating an EGFR TK inhibitor as monotherapy in the treatment of any human malignancy. It is also the largest randomized placebo-controlled study ever conducted in relapsed NSCLC. As second- and third-line therapy for advanced-metastatic NSCLC, erlotinib significantly increased survival relative to placebo (best supportive care). This was associated with delayed deterioration in lung cancer symptoms along with no increased need for palliative medications and radiation. These benefits were not associated with the hematological toxicity commonly seen with standard chemotherapy. The major drug-related adverse events of erlotinib were rash and diarrhea, which were of mild intensity (NCI-CTC Grade 1 or 2) in the majority of affected patients.</p> <p>The findings in this study confirm and strengthen the conclusions from an earlier study (A248-1007) that erlotinib therapy is justified in this patient population and that its benefits in this setting outweigh the risks.</p>		
<p>Date of the Report: 15 JUN 2004</p>		