

CENTER FOR DRUG EVALUATION AND RESEARCH

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21-743

Statistical Review(s)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES
ADDENDUM 1

NDA /Serial Number: 21-743 /N000
Drug Name: Tarceva™ (erlotinib hydrochloride, OSI-774)
Applicant: OSI Pharmaceuticals
Indication(s): Metastatic Non-small Cell Lung Cancer
Date(s): Submission Date: July 30, 2004
PDUFA Date: January 30, 2005
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Review Priority: Priority

Biometrics Division: Division of Biometrics I (HFD-710)
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Project Manager: Mr. Paul Zimmerman

Keywords: Superiority, log-rank test, Cox regression, QoL

In this addendum additional exploratory analyses with respect to smoking history in the Study BR.21 are presented. These analyses do not change the conclusions and recommendations of the review.

The following table shows the baseline characteristics in patients with smoking history and without smoking history.

Table 1: Demographics and Baseline Characteristics of Patients by Smoking History

Characteristic	Smokers		Non-smokers	
	Tarceva (N=358)	Placebo (N=187)	Tarceva (N = 78)	Placebo (N = 49)
Sex: Female	107 (29.9%)	55 (29.4%)	60 (57.7%)	23 (54.8%)
Male	251 (70.1%)	132 (70.6%)	44 (42.3%)	19 (45.2%)
Race: Black	11 (3.1%)	10 (5.4%)	5 (4.8%)	2 (4.8%)
White	292 (81.6%)	153 (81.8%)	65 (62.5%)	26 (61.9%)
Oriental	36 (10.1%)	16 (8.6%)	25 (24.0%)	9 (21.4%)
Others	19 (5.3%)	8 (4.3%)	9 (8.7%)	5 (11.9%)
Age: <= 60 yrs	160 (44.7%)	98 (52.4%)	56 (53.9%)	23 (54.8%)
61-69 yrs	129 (36.0%)	56 (29.9%)	24 (23.1%)	11 (26.2%)
>= 70 yrs	69 (19.3%)	33 (17.7%)	24 (23.1%)	8 (19.0%)
EGFR Status: positive	58 (16.2%)	35 (18.7%)	18 (17.3%)	12 (28.6%)
negative	53 (14.8%)	32 (17.1%)	19 (18.3%)	5 (11.9%)
Unknown	247 (69.0%)	120 (64.2%)	67 (64.4%)	25 (59.5%)
Histology: Adeno	163 (45.5%)	80 (42.8%)	76 (73.1%)	33 (78.6%)
Squamous	122 (34.1%)	67 (35.8%)	11 (7.5%)	4 (9.5%)
MNSC	8 (2.2%)	2 (1.1%)	2 (1.9%)	0 (0.0%)
UNLC	32 (8.9%)	20 (10.7%)	5 (4.8%)	2 (4.8%)
Other	33 (9.2%)	18 (9.6%)	10 (9.6%)	3 (7.1%)
PS: 0-1	244 (68.2%)	128 (68.5%)	74 (71.2%)	25 (59.5%)
2-3	114 (31.8%)	59 (31.5%)	30 (28.8%)	17 (40.5%)
Prior Response: Yes	142 (39.7%)	74 (39.6%)	37 (35.6%)	12 (28.6%)
No	216 (60.3%)	113 (60.4%)	67 (64.4%)	30 (71.4%)
Prior Tx: One	182 (50.8%)	97 (51.9%)	52 (50.0%)	20 (47.6%)
Two	176 (49.2%)	90 (48.1%)	52 (50.0%)	22 (52.4%)
Prior Platinum: No	28 (7.8%)	15 (8.0%)	7 (6.7%)	3 (7.1%)
Yes	330 (92.2%)	172 (92.0%)	97 (93.3%)	39 (92.9%)

Reviewer's Comments:

1. The patients characteristics appear to be balanced between the treatment arms within the subgroup of patients with smoking history (except for age group), and within the subgroup of patients with no smoking history (except for EGFR positive status, performance status and response to prior therapy).
2. There is however a difference between the subgroups with respect to the distribution of gender, race and histology.
3. Results from analyses adjusting for imbalances within each of the two subgroups were similar to the unadjusted analyses:
Smoking Group: HR = 0.865, 95% CI: 0.713, 1.050 Unadjusted analysis;
 HR = 0.866, 95% CI: 0.713, 1.052 Adjusted for age group analysis.
Non-smoking Group: HR = 0.422, 95% CI: 0.278, 0.640 Unadjusted analysis;
 HR = 0.422, 95% CI: 0.296, 0.645 Adjusted for performance status, response to prior therapy and EGFR status.

Further analyses of difference between patients with smoking history versus no smoking history in each of the treatment arms are presented below.

Table 2: Survival Analyses Results in Tarceva Treated Patients

Smoking History Known Population	Smokers N=358	Non-smokers N=104	Hazard Ratio¹ (95% CI)	P-value²
# of Deaths	292	64	1.860 (1.418,2.441)	< 0.0001
Med. Survival in months (95% CI)	5.5 (4.7, 6.5)	12.3 (10.6, 16.1)		

¹Hazard Ratio = Smokers / Non-smokers; ²Unadjusted, log-rank test.

Table 3: Survival Analyses Results in Placebo Treated Patients

Smoking History Known Population	Smokers N=187	Non-smokers N=42	Hazard Ratio¹ (95% CI)	P-value²
# of Deaths	160	37	0.989 (0.691, 1.417)	0.9532
Med. Survival in months (95% CI)	4.6 (3.9, 6.2)	5.6 (3.5, 8.0)		

¹Hazard Ratio = Smokers / Non-smokers; ²Unadjusted, log-rank test.

Reviewer's comment:

The non-smokers appear to benefit more from Tarceva compared to smokers.

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/s/

Rajeshwari Sridhara
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation Research
Office of Pharmacoepidemiology and Statistical Science
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1 Executive Summary

1.1 Conclusions and Recommendations

In this reviewer's opinion the study results from a single, randomized, multicenter, double-blinded, placebo-controlled phase III trial support the claim of efficacy based on overall survival of Tarceva™ (erlotinib hydrochloride) for patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

1.2 Brief Overview of Clinical Studies

This submission consists of results of one phase III, randomized, placebo-controlled, double-blinded clinical trial (registration trial BR.21, referred as BR.21 here after) comparing OSI-774 (Tarceva™, referred as erlotinib here after) versus placebo in patients with incurable stage IIIB/IV non-small cell lung cancer (NSCLC) who have failed standard therapy for advanced or metastatic disease. The sponsor has also provided supportive efficacy data from a phase II, single arm study (A248-1007) of erlotinib following failure of platinum based combination chemotherapy in patients with advanced NSCLC. In addition the sponsor has also submitted results of two phase III, randomized, double-blinded, multicenter trials (Study OSI2298g and Study BO16411) of erlotinib plus chemotherapy (carboplatin + paclitaxel, and cisplatin + gemcitabine, respectively) vs. chemotherapy alone in patients with advanced (stage IIIB/IV) NSCLC who had not received prior chemotherapy. The addition of erlotinib to chemotherapy in both the studies did not demonstrate additional benefit with respect to overall survival compared to chemotherapy alone.

Study BR.21 was a phase III, comparative international study conducted in 731 patients from 86 study centers in 17 countries. Patients ≥ 18 years old with histologically or cytologically confirmed diagnosis of incurable stage IIIB/IV NSCLC who have received at least one but no more than two prior regimens of which at least one had to be combination chemotherapy (if ≥ 70 years old), who had ECOG performance status of 0 to 3, had adequate renal and hepatic functions were randomized in 2:1 ratio to receive either erlotinib (150 mg tablets orally) or placebo. In this study, patients were stratified at randomization by center, number of prior regimens, prior platinum therapy, best response to prior therapy, and ECOG performance status.

1.3 Statistical Issues and Findings

This NDA submission is to support administration of erlotinib in patients with advanced or metastatic NSCLC who have failed at least one prior chemotherapy.

In this NDA submission, study BR.21 is the only randomized pivotal study conducted to establish efficacy. This study enrolled a total of 731 patients with 488 patients who received erlotinib and 243 patients who received placebo. The primary efficacy endpoint of this study was survival. The applicant has submitted this application claiming efficacy based on overall survival. There was a statistically significant difference between the two treatment arms with respect to overall survival in the ITT population (log-rank test, P-value = 0.002, stratified log-rank test, P-value= < 0.0001).

Statistical Issues:

1. The primary analysis of the primary endpoint overall survival was based on stratified log-rank test including randomization stratification factors and EGFR status. In 67% of the patients EGFR status was not evaluated. An adjusted analysis including these 67% patients with missing data on EGFR status is questionable.
2. The results of exploratory analyses in the subgroups suggest a significant survival benefit due to erlotinib in the EGFR positive patients and suggest no survival benefit in the EGFR negative population.

Findings:

The protocol specified primary analysis was stratified log-rank test in the intent-to-treat (ITT) population to compare overall survival between the two treatment arms. This study demonstrates efficacy based on overall survival as presented in the following Table A.

Table A: Primary Efficacy of Overall Survival Analysis in the ITT Population

ITT Population	Placebo N=243	Tarceva N=488	Hazard Ratio ¹ (95% CI)	P-value ²
# of Deaths	209	378	0.764 (0.645, 0.905)	0.0018
Med. Survival in months (95% CI)	4.7 (4.1, 6.3)	6.7 (5.5, 7.8)		

¹ Hazard Ratio = Tarceva / Placebo; ² Unadjusted, log-rank test, adjusted (for randomization stratification factors) analysis p-value < 0.0001

2 Introduction

2.1 Overview

Lung cancer is a common disease in U.S. Currently the treatments approved for the first line therapy of non-small cell lung cancer (NSCLC) Stage IIIB/IV patients are paclitaxel/cisplatin, gemcitabine/cisplatin, and vinorelbine \pm cisplatin. Approved treatments for the second line therapy of NSCLC Stage IIIB/IV patients are docetaxel (approval based on demonstration of survival benefit over best supportive care) and alimta (accelerated approval based on response rate). Iressa was granted accelerated approval for the third line setting of NSCLC Stage IIIB/IV patients based on observed response rate.

2.1.1 Background

Epidermal growth factor receptor (EGFR) and its ligands are overexpressed or involved in autocrine growth loops in a number of tumor types, including NSCLC. EGFR is considered an important prognostic indicator in patients with epithelial malignancies. Increased EGFR expression is correlated with aggressive morphology, poor outcome in NSCLC, and poor response to therapy. Erlotinib acts through direct and reversible inhibition of the EGFR tyrosine kinase, and it inhibits the EGF-dependent proliferation of cells at nanomolar concentrations and blocks cell cycle progression at the G1 phase.

In this application the sponsor has submitted results of 4 studies in NSCLC patients and 5 studies in other tumor types. Study BR.21 is submitted as the registration study.

2.1.2 Statistical Issues

1. The primary analysis of the primary endpoint overall survival was based on stratified log-rank test including randomization stratification factors and EGFR status. In 67% of the patients EGFR status was not evaluated. An adjusted analysis including these 67% patients with missing data on EGFR status is questionable.
2. The results of exploratory analyses in the subgroups suggest a significant survival benefit due to erlotinib in the EGFR positive patients and suggest no survival benefit in the EGFR negative population.

2.2 Data Sources

Data and reports used for review are from the electronic submission received on 5/12/04, 6/22/04 and 7/29/04 The network paths are:

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\\Cdsub1\N21743\N_000\2004-06-22\crt\datasets\BR21 ,
\\Cdsub1\N21743\N_000\2004-06-22\clinstat\lung\BR21 ,
\\Cdsub1\N21743\N_000\2004-07-29\clinstat\lung\ise , and
\\Cdsub1\N21743\N_000\2004-09-17 .

3 Statistical Evaluation

3.1 Evaluation of Efficacy

The sponsor has submitted efficacy results from the following 4 studies conducted in NSCLC patients:

(a) The registration Study BR.21 was a multicenter, international, double-blinded, randomized, phase III trial of erlotinib 150 mg tablet/day versus placebo tablet/day (matched to erlotinib in color, shape, size and packaging) for locally advanced or metastatic NSLC patients who had failed at least one but no more than two prior chemotherapy regimens. The trial treatment was continued until disease progression or unacceptable toxicity. First patient was entered in this Study BR.21 on November 1, 2001 and the last patient was entered on January 31, 2003. The data cut-off date for this application was January 30, 2004. A detailed statistical evaluation of efficacy evidence of this study is presented in section 3.1.1 of this review.

(b) Study A248-1007 was a multicenter, open-label, phase II single arm trial of erlotinib 150 mg tablet/day following failure of platinum based combination chemotherapy in EGFR-positive patients with advanced NSCLC. The trial treatment was taken until disease progression, or unmanageable toxicity. First patient was entered in this Study A248-1007 on January 25, 2000 and the last patient was entered on February 14, 2001. The data cut-off date for this application was January 27, 2003. Results from Study A248-1007 were submitted as supportive evidence to Study BR.21. A summary of the efficacy findings of this study is presented in section 3.1.2 of this review.

(c) Study OSI2298g was a randomized, double-blinded, multicenter, Phase III comparative trial of erlotinib in combination with chemotherapy (paclitaxel and carboplatin) versus chemotherapy alone in patients with advanced (stage IIIB or IV) NSCLC who have not received prior chemotherapy. This study was initiated

on July 18, 2001 and completed on July 11, 2003. A summary of the efficacy findings of this study is presented in section 3.1.3 of this review.

(d) Study BO16411 was a randomized, double-blinded, placebo-controlled, multicenter, Phase III comparative trial of erlotinib in combination with chemotherapy (gemcitabine and cisplatin) versus chemotherapy alone in patients with advanced (stage IIIB or IV) NSCLC who have not received prior chemotherapy. A summary of the efficacy findings of this study is presented in section 3.1.3 of this review.

3.1.1 Study BR.21

3.1.1.1 Study Design

Study BR.21 was a phase III, randomized, placebo-controlled, double-blinded clinical trial comparing erlotinib to placebo. Patients ≥ 18 years old with histologically or cytologically confirmed diagnosis of incurable stage IIIB/IV NSCLC who have received at least one but no more than two prior regimens of which at least one had to be combination chemotherapy (if ≥ 70 years old), who had ECOG performance status of 0 to 3, had adequate renal and hepatic functions were randomized in 2:1 ratio to receive either erlotinib (150 mg/day tablets orally) or placebo ("150 mg"/day tablets matched to erlotinib in color, shape, size and packaging). In this study, patients were stratified at randomization by center, number of prior regimens, prior platinum therapy, best response to prior therapy, and ECOG performance status. Patients were treated until documented progressive disease or until development of intolerable toxicity. Dose escalation was not permitted. The prescribed dose was self-administered, taken 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.

Efficacy was evaluated by periodic assessments (Appendix 1) of survival and QoL scores. Tumor measurements were evaluated every 8 weeks. Safety was assessed every 4 weeks.

[] formerly [] generated randomization codes and managed the [] interactive voice response system (IVRS). The IVRS minimized potential imbalances between treatment arms, based on the above stated 5 stratification factors using a dynamic minimization technique. Therapy began within 2 working days after randomization and patients were considered on treatment until study drug was discontinued.

3.1.1.2 Study Objectives

The primary objective of this study was to compare overall survival between the two treatment arms (erlotinib vs. placebo).

The secondary objectives included comparison of (1) progression-free survival (PFS), (2) response rates (RR), (3) response duration, (4) nature, severity, and frequency of toxicities, and (5) quality of life (QoL) as measured by the European Organization for the Research and Treatment of Cancer (EORTC) quality of life questionnaires QLQ-C30 and the lung cancer module QLQ-LC13. The objectives also included to correlate the expression of tissue EGFR levels (at diagnosis) with outcomes and response to treatment, and to measure and correlate trough levels of erlotinib with clinical responses and /or adverse events.

3.1.1.3 Efficacy Endpoints

Primary Efficacy Endpoint of this study was survival (OS) defined as the time from the date of randomization to the date of death from any cause. Survival time was censored at the date of last post-therapy follow-up visit for patients who were still alive.

Secondary Efficacy Endpoints included:

- (1) PFS defined as the length of time from randomization to the first observation of disease progression or death due to any cause.
- (2) Objective response, determined using RECIST criteria (Appendix 2).
- (3) Duration of response was measured from the time measurement criteria for CR/PR were first met until the first date that recurrent or progressive disease or death was objectively documented.
- (4) QoL, assessed by the EORTC QLQ-30 and QLQ-LC13, with the emphasis on the three pre-specified symptoms (cough, dyspnea, and pain) (Appendix 3).

Reviewer's Comment:

1. All patients who had measurable lesions and who had at least one objective tumor assessment after baseline were considered as evaluable for response.
2. All patients who had completed quality of life assessments were evaluable for QoL.
3. The protocol does not specifically emphasize on the three QoL symptoms, cough, dyspnea and pain. These were added as pre-specified symptoms in the statistical analysis plan and study report.

3.1.1.4 Sample Size Considerations

The study was planned to enroll 700 patients. With this sample size, the study was powered to detect a 33% increase in overall survival time (median survival of 4 months to 5.3 months, hazard ratio (HR) of 1.33) in the erlotinib arm compared to placebo arm with 90% power and maintaining a family-wise two-sided type I error rate of 0.05. The final analysis was planned to be conducted when 582 deaths were observed.

Reviewer's Comments:

1. In the original protocol (dated September 10, 2001) the sample size was determined to be 330 patients with the planned final survival analysis when 256 deaths occurred. This calculation was based on detecting a 50% improvement in survival for erlotinib (6 months vs. 4 months, HR = 1.5) with 90% power using two-sided 5% level of significance. The sample size was amended (amendment dated August 29, 2002) to be 700 patients in order to detect a 33% improvement instead of 50% improvement. It was stated that because of the lack of demonstrable benefit in adding Iressa to standard chemotherapy for NSCLC in the first line setting as reported by AstraZeneca in their press release dated August 19, 2002, and the rapid accrual to study BR.21, that it was decided to increase the sample size to be able to detect a smaller but clinically relevant improvement in survival.
2. The actual number of patients entered on this study was 731 patients.

3.1.1.5 Interim Analysis

No interim analysis was planned for this study.

3.1.1.6 Efficacy Analysis Methods

The primary efficacy analysis was to compare overall survival time using log-rank test stratified by all stratification factors except center plus patient's EGFR status (positive/mutated vs. unknown vs. negative) at baseline in all the randomized patients (ITT population). Kaplan-Meier curves were to be used to display the survival curves and 95% confidence intervals for the median survival computed using the method of Brookmeyer and Crowley. In addition, the effect of study center and other potential prognostic factors on overall survival was planned to be assessed using Cox regression. Additional supporting analysis was to include Kaplan-Meier estimation.

Progression-free survival (PFS) was specified as one of the secondary endpoints. PFS was defined as the time from randomization to the first observation of

disease progression or death due to any cause. A patient who stopped treatment with study drug and went on to receive alternative therapy for NSCLC, prior to documentation of disease progression, was planned to be censored on the date alternative therapy began. Same methods as used in overall survival analysis were to be employed to analyze PFS data.

The secondary endpoint of response rate was planned to be estimated as the proportion of patients evaluable for response who met the criteria of complete or partial response. A Cochran-Mantel-Haenzel test was to be used to compare the tumor response rate between the two treatment arms adjusting all stratification factors, except center plus patient's EGFR status. Duration of response was planned to be analyzed using similar methods as described for overall survival.

The EORTC QLQC30 (Appendix 4) that was used in this study is a self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functioning domains, a global quality of life domain, three symptom domains and six single items. For each domain or single item measure a linear transformation was to be applied to standardize the raw score to range between 0 and 100. The QLQ-LC13 (Appendix 5) lung cancer module which was also used in this study includes questions assessing lung cancer-associated symptoms (cough, haemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. The protocol specified that the questionnaires would be scored as described in QLQ-C30 manual, and analyzed accordingly. The protocol specified that the method of analysis of variance for repeated measures was planned to be used for domains represented by aggregate scores. Questionnaires for patients had to be completed at baseline and every 4 weeks while on study drug. A final questionnaire had to be completed within 2 weeks of progressive disease, or it would be considered completed at the 4-week visit after the end of treatment if it had not already been completed within 2 weeks of progressive disease.

In the statistical analysis plan it was specified that the primary endpoints in the quality of life analysis were defined as the time from randomization to deterioration in the following three QoL symptoms: cough (Question 1 in QLQ-LC13), dyspnea (Question 8 in QLQ-C30) and pain (Questions 1 and 19 in QLQ-C30). Patients were considered as deteriorated for a given symptom if their change of 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. It was stated in the statistical analysis plan that the value of 10 points on a 100 scale was chosen as previous studies had indicated that a 10% change of highest possible score are perceived as clinically significant.

The statistical analysis plan stated that for each symptom, all patients who had a baseline and at least one of the follow-up QoL assessments for the symptom would be included in the time to deterioration analysis. Patients would be censored at the time of the last QoL questionnaire completion if they had not deteriorated before that. Unstratified log-rank test would be used as the primary method to compare the time to deterioration in each symptom between the two treatment arms. The Hochberg procedure was planned to be used to adjust the p-values of the log-rank tests for these three comparisons.

Reviewer's Comment:

The primary endpoints and the method of QoL analysis was specified differently in the statistical analysis plan which was finalized on June 11, 2003, after all patients had been entered on the study. Given that this was a secondary endpoint and the analysis plan was finalized after the completion of accrual to the study (last patient entered on January 31, 2003) analysis of QoL data can only be considered as exploratory.

3.1.1.7 Sponsor's Results and Statistical Reviewer's Findings/ Comments

In the BR.21 study, a total 731 patients with advanced or metastatic NSCLC were entered into the study across 86 study sites, 27 in Canada, 1 in US and 58 internationally (rest of the world). The overall survival efficacy analysis submitted in this NDA was based on 488 patients in erlotinib treatment arm and 243 patients in placebo arm. A total of 7 patients were declared as lost to follow-up (4 patients in the erlotinib arm and 3 patients in the placebo arm). The sponsor has reported some discrepancies between the data provided by the center to obtain randomization and the actual baseline data. Of note, response to prior chemotherapy at baseline was better than was reported at randomization for 26 patients (5%) in the erlotinib arm and for 9 patients (4%) in the placebo arm, and it was worse for 57 patients (12%) and 22 patients (9%) in the erlotinib and placebo arms respectively.

3.1.1.7.1 Baseline Characteristics

The baseline Characteristics of the overall population are presented in Table 1.

Reviewer's Comment:

In the overall patient population the baseline characteristics appear to be balanced between the two treatment arms.

Table 1: Demographics and Baseline Characteristics of Patients

Characteristic	Tarceva (N = 488)	Placebo (N = 243)
Sex: Female	173 (35.5%)	83 (34.2%)
Male	315 (64.5%)	160 (65.8%)
Race: Black	18 (3.7%)	12 (4.9%)
White	379 (77.7%)	188 (77.4%)
Oriental	63 (12.9%)	28 (11.5%)
Others	28 (5.7%)	15 (6.2%)
Age: ≤ 60 yrs	225 (46.1%)	131 (53.9%)
61-69 yrs	166 (34.0%)	69 (28.4%)
≥ 70 yrs	97 (19.9%)	43 (17.7%)
Smoking history: No	104 (21.4%)	42 (17.4%)
Yes	358 (73.7%)	187 (77.3%)
Unknown	26 (5.3%)	14 (5.8%)
Histology: Adenocarcinoma	246 (50.4%)	119 (48.9%)
Squamous Cell	144 (29.5%)	78 (32.1%)
Mixed Non-small cell	11 (2.3%)	2 (0.8%)
Undifferentiated large cell	41 (8.4%)	23 (9.5%)
Other	46 (9.4%)	21 (8.6%)
ECOG performance status: 0-1	326 (66.8%)	163 (67.1%)
2-3	162 (33.2%)	80 (32.9%)
Prior Response: Yes	186 (38.1%)	92 (37.9%)
No	302 (61.9%)	151 (62.1%)
Prior Therapy: One	247 (50.6%)	122 (50.2%)
Two	241 (49.4%)	121 (49.8%)
Prior Platinum: No	39 (8.0%)	20 (8.2%)
Yes	449 (92.0%)	223 (91.8%)
EGFR: Negative	74 (15.2%)	37 (15.2%)
Positive	78 (16.0%)	49 (20.2%)
Unknown	24 (4.9%)	10 (4.1%)
No Sample	312 (63.9%)	147 (60.5%)

Baseline PS, prior response, prior number of therapy, prior platinum treatment were stratification factors at baseline (characteristics in blue; using data variables alaecog, alabrsp, alareg and alaplat in patient.xpt data set).

3.1.1.7.2 Primary Efficacy Analyses

Primary efficacy analysis was overall survival analysis using stratified log-rank test. At the time of this analysis presented in this NDA a total of 587 deaths were observed (final analysis planned with 582 deaths). The results of the survival analysis based on ITT population using unadjusted log-rank test are presented in

Table 2 (same as reported by the sponsor). The results of the stratified log-rank test, primary analysis as specified in the protocol, were similar to the unadjusted analysis (adjusted p-value < 0.0001). The results of adjusted analysis using Cox regression as specified in the protocol are presented in Table 3. The Kaplan-Meier curves of the overall survival in the ITT population are illustrated in Figure 1.

Table 2: Primary Efficacy of Overall Survival Analysis in the ITT Population

ITT Population	Placebo N=243	Tarceva N=488	Hazard Ratio ¹ (95% CI)	P-value ²
# of Deaths	209	378	0.764 (0.645, 0.905)	0.0018
Med. Survival in months (95% CI)	4.7 (4.1, 6.3)	6.7 (5.5, 7.8)		

¹Hazard Ratio = Tarceva / Placebo; ²Unadjusted, log-rank test, adjusted (for randomization stratification factors) analysis p-value < 0.0001

Figure 1: Kaplan-Meier Survival Curves in the ITT Population

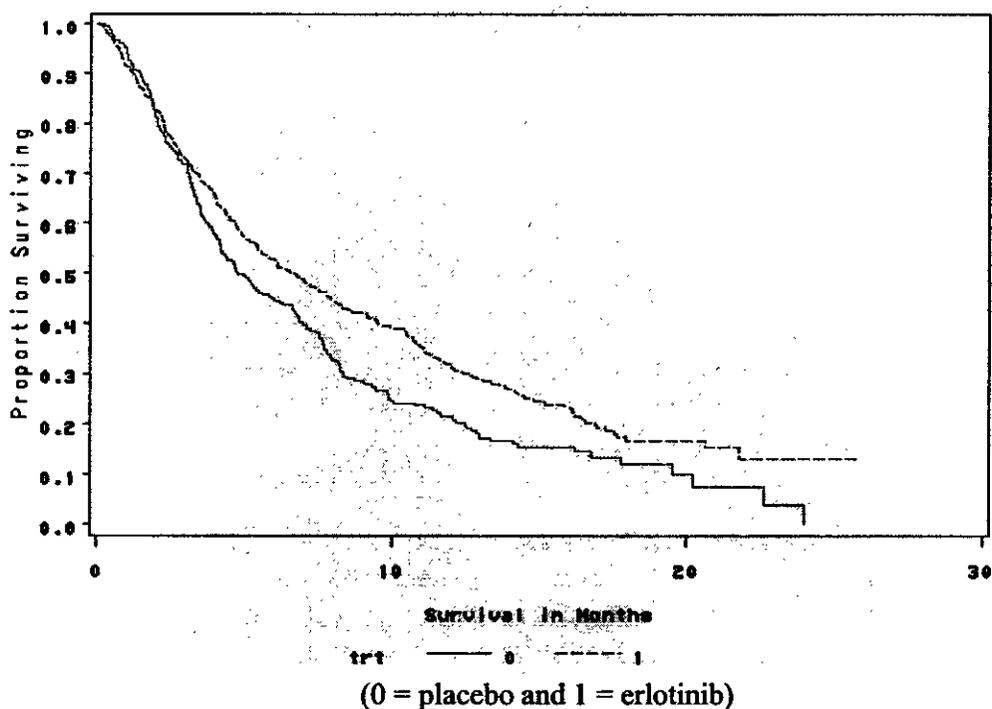


Table 3: Cox Regression Analysis in the ITT Population Adjusting for Randomized Stratification Factors and Baseline EGFR Status (Protocol Specified Analysis)

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.726	0.612, 0.861	0.0002
Baseline ECOG PS (2-3 vs. 0-1)	1.895	1.593, 2.254	<0.0001
Response to prior therapy (SD vs. CR/PR + PD)	0.915	0.752, 1.113	0.3725
(PD vs. CR/PR + SD)	1.356	1.104, 1.666	0.0037
Number of prior therapy (2 vs. 1)	1.136	0.959, 1.346	0.1413
Prior platinum therapy (no vs. yes)	0.663	0.484, 0.909	0.0105
EGFR Status			
Negative vs. Positive + Unknown	1.142	0.854, 1.527	0.3695
Unknown vs. Negative + Positive	1.169	0.930, 1.470	0.1814

*P-value by stratified log-rank including stratification factors and EGFR status was also < 0.0001.

Reviewer's Comments:

1. The final analysis of the overall survival demonstrates superiority of erlotinib over placebo with respect to overall survival (Table 2 and Figure 1).
2. It should be noted that there were no events observed in some of the strata and thus the results of the adjusted analyses should be interpreted with caution.
3. In about 67% of the patients EGFR status was unknown at baseline. Including EGFR status in the model amounts to categorizing the unknown group as another category (as if it was an intermediate category between positive and negative status). However the unknown EGFR status includes patients who were not assessed for EGFR status (missing data) and would in fact be either EGFR positive or negative. Thus the results of the model including EGFR status are not interpretable.
4. It should also be noted that more than 90% of the patients had received prior platinum therapy in both the treatment arms and thus adding it as a covariate in the model may not add to the interpretation of the treatment effect.
5. Results of Cox regression analysis including only the randomized stratification factors are presented in Tables 4 and 5.
6. Results of Cox regression analysis including the stratification factors and baseline AAG levels (identified as important prognostic factor in literature; also refer to Clinical pharmacology review) are presented in Table 6.
7. All the analyses suggest that the treatment effect is significant and the hazard ratios range from 0.73 to 0.76.

Table 4: Cox Regression Analysis in the ITT Population Adjusting for Randomized Stratification Factors (Prior Response 2 Categories)

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.732	0.617, 0.868	0.0003
Baseline ECOG PS (2-3 vs. 0-1)	1.977	1.665, 2.347	<0.0001
Response to prior therapy (SD/PD vs. CR/PR)	1.094	0.924, 1.297	0.2973
Number of prior therapy (2 vs. 1)	1.120	0.951, 1.319	0.1754
Prior platinum therapy (no vs. yes)	0.652	0.477, 0.890	0.0071

*P-value not adjusted for multiplicity

Table 5: Cox Regression Analysis in the ITT Population Adjusting for Randomized Stratification Factors (Prior Response 3 Categories)

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.727	0.613, 0.862	0.0003
Baseline ECOG PS (2-3 vs. 0-1)	1.896	1.594, 2.254	<0.0001
Response to prior therapy (SD vs. CR/PR + PD)	0.926	0.762, 1.126	0.4418
(PD vs. CR/PR + SD)	1.386	1.131, 1.699	0.0017
Number of prior therapy (2 vs. 1)	1.105	0.938, 1.301	0.2331
Prior platinum therapy (no vs. yes)	0.646	0.473, 0.883	0.0061

*P-value not adjusted for multiplicity

Table 6: Cox Regression Analysis in the ITT Population Adjusting for Randomized Stratification Factors, Baseline EGFR Status and AAG levels

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.730	0.609, 0.875	0.0007
Baseline ECOG PS (2-3 vs. 0-1)	1.546	1.277, 1.870	< 0.0001
Response to prior therapy (SD vs. CR/PR + PD)	0.919	0.745, 1.134	0.4310
(PD vs. CR/PR + SD)	1.344	1.083, 1.667	0.0072
Number of prior therapy (2 vs. 1)	1.159	0.967, 1.389	0.1100
Prior platinum therapy (no vs. yes)	0.703	0.501, 0.987	0.0416
EGFR Status			
Negative vs. Positive + Unknown	1.037	0.769, 1.399	0.8124
Unknown vs. Negative + Positive	1.071	0.845, 1.356	0.5719
Baseline AAG**	1.988	1.698, 2.328	< 0.0001

*P-value not adjusted for multiplicity; ** Continuous variable; Analysis based on data from 659 patients.

3.1.1.7.3 Exploratory Survival Analyses

This reviewer conducted several exploratory analyses as presented below. The analyses presented in this section are considered as supportive/hypothesis generating, and none of them are adjusted for multiplicity.

The sponsor has stated that the mechanism of action of erlotinib is through direct inhibition of the EGFR tyrosine kinase. Therefore, this reviewer examined the relationship between EGFR status and treatment effect. EGFR expression status was determined by LabCorp using the DAKO EGFR pharmDX™ kit. A positive EGFR expression was defined as having at least 10% of cells staining for EGFR. Among the patients whose EGFR status was evaluated, there were 127 patients who were EGFR positive and 111 patients who were EGFR negative by the above criteria. The baseline characteristics of these two subgroups of patients are presented in Tables 7 and 8.

Table 7: Demographics and Baseline Characteristics of EGFR Positive Patients

Characteristic	Tarceva (N = 78)	Placebo (N = 49)
Sex: Female	22 (28.2%)	20 (40.8%)
Male	56 (71.8%)	29 (59.2%)
Race: Black	3 (3.9%)	4 (8.2%)
White	67 (85.9%)	41 (83.7%)
Oriental	5 (6.4%)	3 (6.1%)
Others	3 (3.9%)	1 (2.0%)
Age: ≤ 60 yrs	25 (32.1%)	24 (49.0%)
61-69 yrs	33 (42.3%)	16 (32.6%)
≥ 70 yrs	20 (25.6%)	9 (18.4%)
Smoking history: No	18 (23.4%)	12 (24.5%)
Yes	58 (75.3%)	35 (71.4%)
Unknown	2 (2.6%)	2 (4.1%)
Histology: Adeno	39 (50.0%)	29 (59.2%)
Squamous	26 (33.3%)	15 (30.6%)
MNSC	2 (2.6%)	0 (0.0%)
UNLC	8 (10.3%)	2 (4.1%)
Other	3 (3.8%)	3 (6.1%)
PS: 0-1	52 (66.7%)	29 (59.2%)
2-3	26 (33.3%)	20 (40.8%)
Prior Response: Yes	42 (53.9%)	18 (36.7%)
No	36 (46.1%)	31 (63.3%)
Prior Tx: One	24 (30.8%)	18 (36.7%)
Two	54 (69.2%)	31 (63.3%)
Prior Platinum: No	8 (10.3%)	5 (10.2%)
Yes	70 (89.7%)	44 (89.8%)

Table 8: Demographics Baseline Characteristics in EGFR Negative population

Characteristic	Tarceva (N = 74)	Placebo (N = 37)
Sex: Female	34 (46.0%)	15 (40.5%)
Male	40 (54.0%)	22 (59.5%)
Race: Black	5 (6.8%)	4 (10.8%)
White	63 (85.1%)	30 (81.1%)
Oriental	4 (5.4%)	2 (5.4%)
Others	2 (2.7%)	1 (2.7%)
Age: <= 60 yrs	41 (55.4%)	21 (56.8%)
61-69 yrs	26 (35.1%)	11 (29.7%)
>= 70 yrs	7 (9.5%)	5 (13.5%)
Smoking history: No	19 (25.7%)	5 (13.5%)
Yes	53 (71.6%)	32 (86.5%)
Unknown	2 (2.7%)	0 (0.0%)
Histology: Adeno	45 (60.8%)	18 (48.7%)
Squamous	15 (20.3%)	11 (29.7%)
MNSC	2 (2.7%)	0 (0.0%)
UNLC	5 (6.8%)	4 (10.8%)
Other	7 (9.5%)	4 (10.8%)
PS: 0-1	55 (74.3%)	31 (83.8%)
2-3	19 (25.7%)	6 (16.2%)
Prior Response: Yes	25 (33.8%)	16 (43.2%)
No	49 (66.2%)	21 (56.8%)
Prior Tx: One	30 (40.5%)	18 (48.7%)
Two	44 (59.5%)	19 (51.3%)
Prior Platinum: No	2 (2.7%)	2 (5.4%)
Yes	72 (97.3%)	35 (94.6%)

Reviewer's Comments:

1. There were imbalances observed between the treatment arms in the EGFR positive population. Specifically, imbalances in proportion of females, patients ≤ 60 years, patients with adenocarcinoma and patients who had received only one prior treatment, appear to favor the placebo arm. Imbalances in proportion of patients with ECOG PS 0-1 and patients who had CR/PR to prior therapy appear to favor erlotinib arm.
2. There were also imbalances observed between the treatment arms in the EGFR negative population. Specifically, imbalances in proportion of patients with ECOG PS 0-1, patients who had CR/PR to prior therapy, and patients who had received only one prior treatment appear to favor the

placebo arm. Imbalances in proportion of females, non-smokers and patients with adenocarcinoma appear to favor erlotinib arm.

3. Results of unadjusted analysis comparing survival distributions between the two treatment arms in the EGFR positive, negative and unknown (EGFR status not assessed) are presented in Tables 9 -11 and Figures 2-4. The results of these exploratory analyses in the subgroups, suggest a significant survival benefit in the EGFR positive patients. With this limited data and exploratory analysis, survival benefit due to erlotinib in the EGFR negative population is not observed, although benefit in this subgroup can not ruled out.
4. This reviewer further conducted exploratory analyses adjusting for the stratification factors and imbalances observed in the two subgroups of EGFR positive and negative patients. The results of these adjusted analyses are presented in Tables 12-19. The observed survival benefit due to erlotinib in the EGFR positive patients even after adjusting for imbalances appears to be significant. However, adjusted models in the EGFR negative patients are sensitive to addition or deletion of covariates and erlotinib effect appears to be marginal.
5. To further explore the differences in EGFR positive and negative patients, survival analysis comparing EGFR positive to negative patients in the erlotinib and placebo treated groups was conducted separately (Tables 20 and 21). Although statistically not significant, EGFR positive patients appear to have better survival than the EGFR negative patients in erlotinib treated patients. However EGFR negative patients appear to have better survival compared to EGFR positive patients in the placebo treated patients.
6. Because of the apparent opposite trend observed between erlotinib and placebo patients with respect to EGFR status, Cox regression analysis including an interaction term was conducted in patients with known EGFR status (Tables 22-24). Although the treatment effect was present in all the models, the treatment HR changed by more than 14% when the interaction term was included, suggesting significant interaction effect.

Table 9: Survival Analyses Results in EGFR Positive population

EGFR+ Population	Placebo N=49	Tarceva N=78	Hazard Ratio¹ (95% CI)	P-value²
# of Deaths	42	58	0.646 (0.430, 0.969)	0.0333
Med. Survival in months (95% CI)	3.8 (3.1, 6.8)	10.7 (7.9, 12.8)		

¹Hazard Ratio = Tarceva / Placebo; ²Unadjusted, log-rank test, not adjusted for multiplicity.

Table 10: Survival Analyses Results in EGFR Negative population

EGFR- Population	Placebo N=37	Tarceva N=74	Hazard Ratio ¹ (95% CI)	P-value ²
# of Deaths	30	59	1.012 (0.651, 1.572)	0.9581
Med. Survival in months (95% CI)	7.5 (3.1, 12.0)	5.2 (3.9, 8.2)		

¹Hazard Ratio = Tarceva / Placebo; ²Unadjusted, log-rank test.

Table 11: Survival Analyses Results in EGFR Unknown population

EGFR- Population	Placebo N=157	Tarceva N=336	Hazard Ratio ¹ (95% CI)	P-value ²
# of Deaths	137	261	0.757 (0.614, 0.932)	0.0085
Med. Survival in months (95% CI)	5.1 (4.1, 6.6)	6.0 (4.9, 7.2)		

¹Hazard Ratio = Tarceva / Placebo; ²Unadjusted, log-rank test.

Figure 2: Kaplan-Meier Survival Curves in the EGFR Positive Population

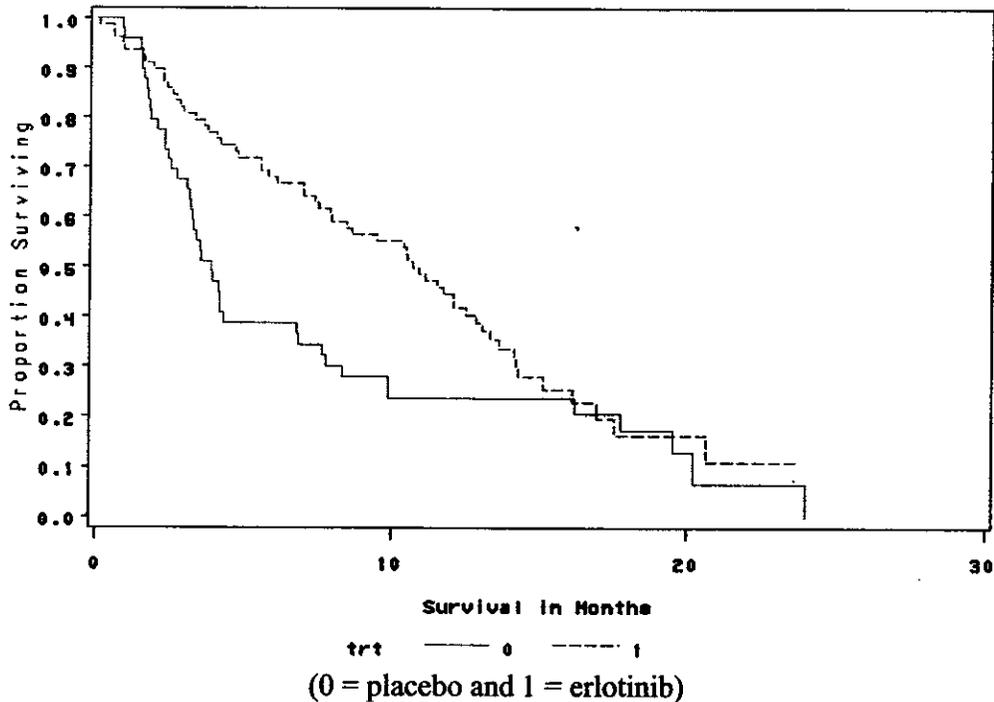


Figure 3: Kaplan-Meier Survival Curves in the EGFR Negative Population

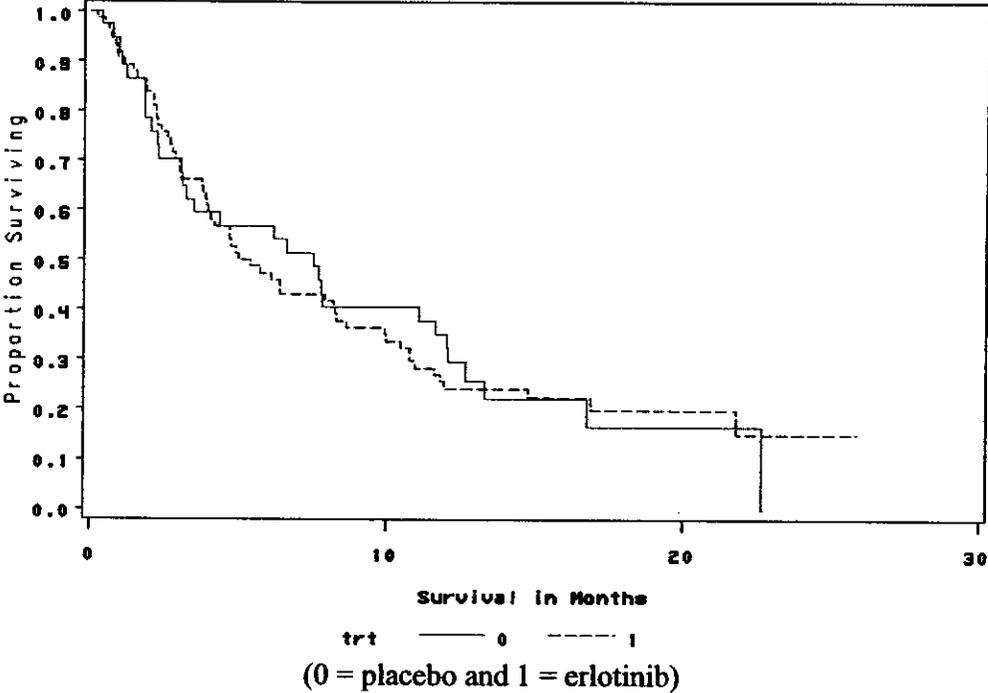


Figure 4: Kaplan-Meier Survival Curves in the EGFR Status Unknown Population

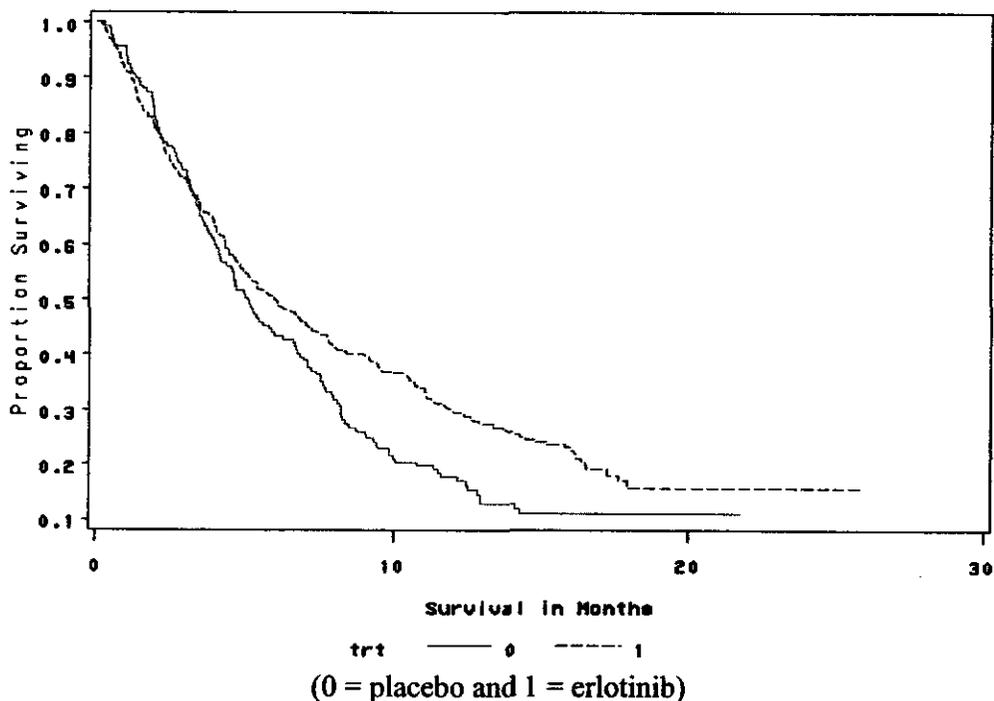


Table 12: Cox Regression Analysis in the EGFR Positive Population Adjusting for Stratification Factors (Prior Response 2 Categories)

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.607	0.401, 0.918	0.0180
Baseline ECOG PS (2-3 vs. 0-1)	2.639	1.722, 4.043	<0.0001
Response to prior therapy (SD/PD vs. CR/PR)	1.255	0.830, 1.899	0.2819
Number of prior therapy (2 vs. 1)	0.906	0.585, 1.405	0.6606
Prior platinum therapy (no vs. yes)	0.280	0.125, 0.628	0.0020

*P-value not adjusted for multiplicity

Table 13: Cox Regression Analysis in the EGFR Positive Adjusting for Randomized Stratification Factors (Prior Response 3 Categories)

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.579	0.381, 0.879	0.0103
Baseline ECOG PS (2-3 vs. 0-1)	2.449	1.584, 3.787	< 0.0001
Response to prior therapy (SD vs. CR/PR + PD)	1.027	0.640, 1.647	0.9127
(PD vs. CR/PR + SD)	1.850	1.082, 3.164	0.0246
Number of prior therapy (2 vs. 1)	0.873	0.563, 1.354	0.5442
Prior platinum therapy (no vs. yes)	0.248	0.109, 0.563	0.0009

*P-value not adjusted for multiplicity

Table 14: Cox Regression Analysis in the EGFR Positive Population Adjusting for Factors Which Appear to be Imbalanced

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.609	0.400, 0.927	0.0205
Baseline ECOG PS (2-3 vs. 0-1)	2.390	1.540, 3.708	0.0001
Response to prior therapy (SD/PD vs. CR/PR)	1.374	0.906, 2.084	0.1348
Number of prior therapy (2 vs. 1)	1.196	0.761, 1.878	0.4373
Age group (> 60 yrs vs. ≤60 yrs)	0.778	0.497, 1.218	0.2725
Sex (male vs. female)	1.202	0.756, 1.909	0.4368
Histology (adeno vs. others)	0.575	0.379, 0.873	0.0093

*P-value not adjusted for multiplicity

Table 15: Cox Regression Analysis in the EGFR Positive Population Adjusting for Factors Which Appear to be Imbalanced and Baseline AAG Levels

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.653	0.425, 1.004	0.0519
Baseline ECOG PS (2-3 vs. 0-1)	2.061	1.295, 3.278	0.0023
Response to prior therapy (SD/PD vs. CR/PR)	1.521	0.996, 2.322	0.0521
Number of prior therapy (2 vs. 1)	1.318	0.830, 2.093	0.2414
Age group (> 60 yrs vs. ≤60 yrs)	0.673	0.421, 1.075	0.0974
Sex (male vs. female)	1.331	0.825, 2.148	0.2410
Histology (adeno vs. others)	0.728	0.468, 1.133	0.1595
Base AAG	3.460	2.233, 5.360	< 0.0001

*P-value not adjusted for multiplicity

**Table 16: Cox Regression Analysis in the EGFR Negative Population
Adjusting for Stratification Factors (Prior Response 2 Categories)**

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.937	0.596, 1.472	0.7764
Baseline ECOG PS (2-3 vs. 0-1)	1.870	1.134, 3.083	0.0142
Response to prior therapy (SD/PD vs. CR/PR)	0.897	0.577, 1.392	0.6265
Number of prior therapy (2 vs. 1)	0.800	0.523, 1.223	0.3018
Prior platinum therapy (no vs. yes)	0.911	0.330, 2.514	0.8568

*P-value not adjusted for multiplicity

**Table 17: Cox Regression Analysis in the EGFR Negative Adjusting for
Randomized Stratification Factors (Prior Response 3 Categories)**

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.958	0.612, 1.498	0.8497
Baseline ECOG PS (2-3 vs. 0-1)	1.643	0.982, 2.748	0.0587
Response to prior therapy (SD vs. CR/PR + PD)	0.724	0.444, 1.180	0.1946
(PD vs. CR/PR + SD)	1.486	0.828, 2.667	0.1846
Number of prior therapy (2 vs. 1)	0.726	0.470, 1.120	0.1479
Prior platinum therapy (no vs. yes)	0.710	0.254, 1.986	0.5137

*P-value not adjusted for multiplicity

**Table 18: Cox Regression Analysis in the EGFR Negative Population
Adjusting for Factors Which Appear to be Imbalanced**

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	1.033	0.652, 1.636	0.8904
Baseline ECOG PS (2-3 vs. 0-1)	1.812	1.083, 3.033	0.0237
Response to prior therapy (SD/PD vs. CR/PR)	1.005	0.638, 1.581	0.9840
Number of prior therapy (2 vs. 1)	0.798	0.511, 1.245	0.3195
Smoking history (yes vs. no)	1.585	0.873, 2.881	0.1304
Sex (male vs. female)	1.009	0.641, 1.589	0.9681
Histology (adeno vs. others)	0.757	0.475, 1.207	0.2418

*P-value not adjusted for multiplicity

**Table 19: Cox Regression Analysis in the EGFR Negative Population
Adjusting for Factors Which Appear to be Imbalanced**

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	1.156	0.715, 1.871	0.5543
Baseline ECOG PS (2-3 vs. 0-1)	1.534	0.888, 2.649	0.1251
Response to prior therapy (SD/PD vs. CR/PR)	0.994	0.630, 1.567	0.9785
Number of prior therapy (2 vs. 1)	0.832	0.522, 1.324	0.4366
Smoking history (yes vs. no)	1.525	0.837, 2.776	0.1678
Sex (male vs. female)	1.098	0.684, 1.763	0.6985
Histology (adeno vs. others)	0.737	0.455, 1.193	0.2140
Baseline AAG	2.019	1.272, 3.204	0.0029

*P-value not adjusted for multiplicity

Table 20: Survival Analyses Results in Tarceva Treated Patients

EGFR Known Population	Positive N=78	Negative N=74	Hazard Ratio ¹ (95% CI)	P-value ²
# of Deaths	58	59	1.345 (0.933,1.937)	0.1100
Med. Survival in months (95% CI)	10.7 (7.9, 12.8)	5.2 (3.9, 8.3)		

¹Hazard Ratio = EGFR- / EGFR+; ²Unadjusted, log-rank test.

Table 21: Survival Analyses Results in Placebo Treated Patients

EGFR Known Population	Positive N=49	Negative N=37	Hazard Ratio ¹ (95% CI)	P-value ²
# of Deaths	42	30	0.870 (0.541, 1.398)	0.5638
Med. Survival in months (95% CI)	3.8 (3.1, 6.8)	7.5 (3.1, 12.0)		

¹Hazard Ratio = EGFR- / EGFR+; ²Unadjusted, log-rank test.

Table 22: Cox Regression Analysis in the EGFR Status Known Population

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.770	0.574, 1.033	0.0817

*P-value not adjusted for multiplicity

Table 23: Cox's Proportional Hazard Model in the EGFR Status Known Population

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.771	0.575, 1.036	0.0841
EGFR Status (- vs. +)	1.099	0.825, 1.464	0.5175

*P-value not adjusted for multiplicity

Table 24: Cox's Proportional Hazard Model in the EGFR Status Known Population

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Tarceva vs Placebo)	0.627	0.420, 0.936	0.0222
EGFR Status (- vs. +)	0.834	0.521, 1.335	0.4498
Interaction between Treatment and EGFR	1.562	0.859, 2.838	0.1435

*P-value not adjusted for multiplicity

3.1.1.7.4 Secondary Efficacy Analyses

The protocol specified secondary endpoints included progression-free survival, objective response (complete response (CR) and partial response (PR)) and duration of response among responders, and QoL endpoints.

3.1.1.7.4.1 Progression-free Survival

Results of unadjusted progression-free survival (data agreed between FDA and sponsor) analysis in the ITT, EGFR positive and EGFR negative populations are presented in Tables 25-27.

Reviewer's Comment:

PFS results are similar to overall survival analysis results. PFS is significantly longer in the erlotinib treated patients both in the ITT and EGFR positive population.

Table 25: Progression-free Survival Analysis in the ITT Population

ITT Population	Placebo N=243	Tarceva N=488	Hazard Ratio ¹ (95% CI)	P-value ²
# of Events	211	402	0.605 (0.510, 0.717)	< 0.0001
Med. Survival in weeks (95% CI)	7.9 (7.7, 8.1)	9.9 (8.4, 14.1)		

¹Hazard Ratio = Tarceva / Placebo; ²Unadjusted, log-rank test (stratified log-rank per SAP p-value < 0.0001), adjusted (for randomization stratification factors) analysis p-value < 0.0001.

Table 26: Progression-free Survival Analysis in the EGFR Positive Population

ITT Population	Placebo N=49	Tarceva N=78	Hazard Ratio ¹ (95% CI)	P-value ²
# of Events	41	64	0.486 (0.326, 0.724)	0.0003
Med. Survival in weeks (95% CI)	7.9 (7.3, 8.4)	16.1 (12.0, 24.0)		

¹Hazard Ratio = Tarceva / Placebo; ²Unadjusted, log-rank test.

Table 27: Progression-free Survival Analysis in the EGFR Negative Population

ITT Population	Placebo N=37	Tarceva N=74	Hazard Ratio ¹ (95% CI)	P-value ²
# of Events	33	62	0.909 (0.594, 1.392)	0.6570
Med. Survival in weeks (95% CI)	8.1 (7.9, 12.0)	8.1 (7.9, 9.4)		

¹Hazard Ratio = Tarceva / Placebo; ²Unadjusted, log-rank test.

3.1.1.7.4.2 Objective Response Rate

There were a total of 41 objective responses (CR + PR) with 39 in the erlotinib arm and 2 in the placebo arm. The response rates with their 95% confidence intervals are presented in Table 28. The median duration of response was 34.3 weeks.

Table 28: Objective Response Rate by Treatment Arm in ITT Population

Response Category	Placebo (N=243)		Erlotinib (N=488)	
	# of Responders	95% CI	# of Responders	95% CI
CR	1 (0.4%)	0.01, 2.3 %	5 (1.0%)	0.3, 2.4 %
PR	1 (0.4%)	0.01, 2.3 %	34 (7.0%)	4.9, 9.6 %
ORR = CR + PR	2 (0.8%)	0.1, 2.9 %	39 (8.0%)	5.7, 10.8 %

Table 29: Characteristics of Responders in Erlotinib Treated Patients

Response Category	Sex	Race	Smoking History	Histology	EGFR Status
CR	3 Males	3 White	2 Smokers 1 Unknown	3 Adenocarcinoma	2 Positive 1 Unknown
	2 Females	1 White 1 Other	2 Non-smokers	2 Adenocarcinoma	1 Positive 1 Unknown
PR	14 Males	12 White 2 Oriental	7 Non-smokers 7 Smokers	10 Adenocarcinoma 2 Squamouscell Ca 1 MNSC 1 Other	2 Positive 1 Negative 11 Unknown
	20 Females	9 White 8 Oriental 3 Other	15 Non-smokers 3 Smokers 2 Unknown	15 Adenocarcinoma 3 Squamouscell Ca 1 MNSC 1 Other	3 Positive 1 Negative 11 Unknown

1 CR and 1 PR were observed in the Placebo group.

Reviewer's Comments:

1. Observed response rates in erlotinib arm are similar to response rates published in literature for docetaxel, Iressa and alimta for this patient population.
2. The characteristics of responders in the erlotinib treated arm are presented in Table 29. Higher response rate was observed in females (22/173 (12.7%), 95% CI: 8.1, 18.6%) compared to males (17/315 (5.4%), 95% CI: 3.2, 8.5%). Similarly higher response rate was observed in oriental patients (10/63 (15.9%), 95% CI: 7.9, 27.3%) compared to White patients (25/379 (6.6%), 95% CI: 4.3, 9.6%). Response rate among smokers was 12/358 (3.4%, 95% CI: 1.7, 5.8%) and among non-smokers response rate was 24/104 (23.1%, 95% CI: 15.4, 32.4%). Response rate in EGFR positive patients was 8/78 (10.3%, 95% CI: 4.5, 19.2%) and response rate in EGFR negative patients was 2/74 (2.7%, 0.3, 9.4%).

3.1.1.7.4.3 Quality of Life Endpoints

Table 30 summarizes the sponsor's baseline QoL assessments for cough, dyspnea and pain symptoms. Baseline scores for each of the three symptoms were well balanced between two treatment arms. Maximal cough was reported by 5% of the patients in the erlotinib and placebo arm at baseline, as was dyspnea. Maximum pain was reported by 3% and 5% of the patients in the erlotinib and placebo arms, respectively.

Table 30: Summary of Baseline QoL Assessments for Cough, Dyspnea and Pain

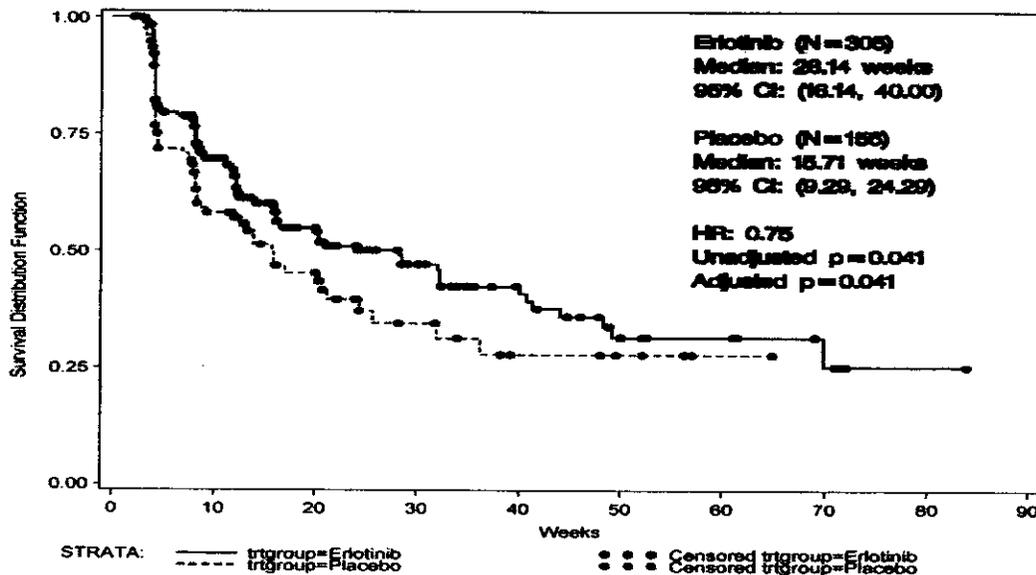
Symptom and range of Scores	Erlotinib (N=488)		Placebo (N=243)	
	n	(%)	n	(%)
Cough	305	(63)	156	(64)
0	52	(11)	39	(16)
33	140	(29)	66	(27)
67	91	(19)	39	(16)
100	22	(5)	12	(5)
Dyspnea	360	(74)	182	(75)
0	116	(24)	62	(26)
33	143	(29)	75	(31)
67	79	(16)	32	(13)
100	22	(5)	13	(5)
Pain	363	(74)	182	(75)
0	95	(19)	39	(16)
17	81	(17)	39	(16)
33	74	(15)	37	(15)
50	40	(8)	22	(9)
67	40	(8)	19	(8)
83	17	(3)	14	(6)
100	16	(3)	12	(5)

Time to Deterioration of Cough

Deterioration of cough at some time after baseline was reported for 131/305 patients in the erlotinib arm (43%) and for 71/156 patients (46%) in the placebo arm. Time to deterioration of cough is displayed in Figure 1 (Sponsor's analysis). The medians were 28.14 weeks in the erlotinib arm and 15.71 weeks in the placebo arm, unadjusted p-value = 0.041, Hochberg adjusted p-value = 0.041. The

HR for deterioration of cough in the erlotinib arm relative to the placebo arm was 0.75 (95% CI, 0.56 - 1.00).

Figure 5: Time to Deterioration of Cough

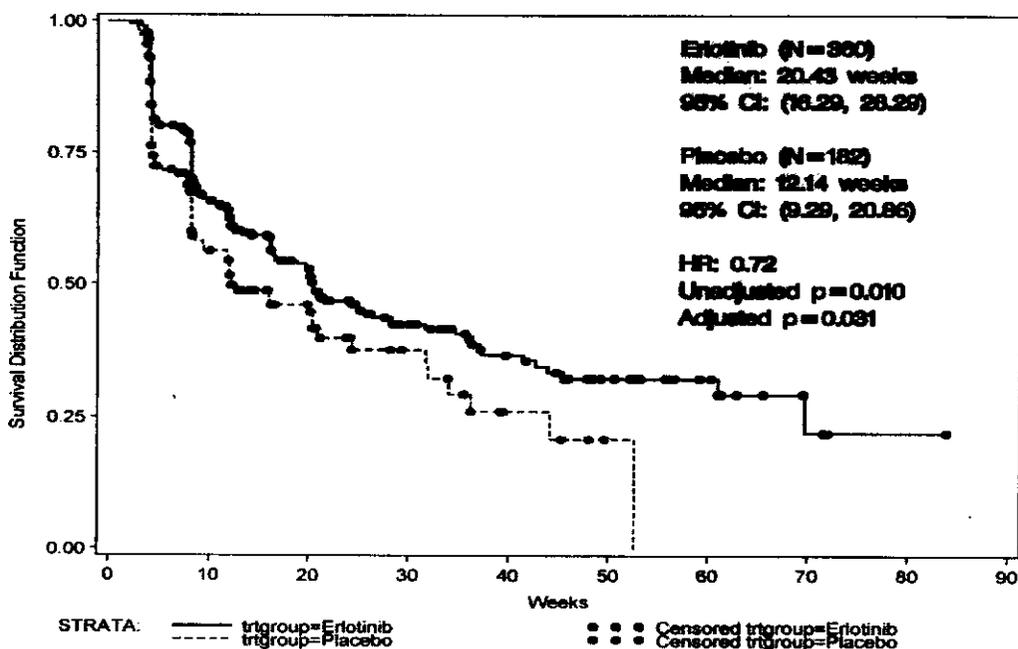


Time to Deterioration of Dyspnea

Deterioration of dyspnea at some time after baseline was reported for 172/360 patients in the erlotinib arm (48%) and for 90/182 patients (49%) in the placebo arm. Time to deterioration of dyspnea is displayed in Figure 2 (Sponsor's analysis). The median times were 20.43 weeks in the erlotinib arm and 12.14 weeks in the placebo arm, unadjusted p-value = 0.010, adjusted p-value = 0.031. The HR for deterioration of dyspnea in the erlotinib arm relative to the placebo arm was 0.72 (95% CI, 0.56 - 0.93).

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Figure 6: Time to Deterioration of Dyspnea

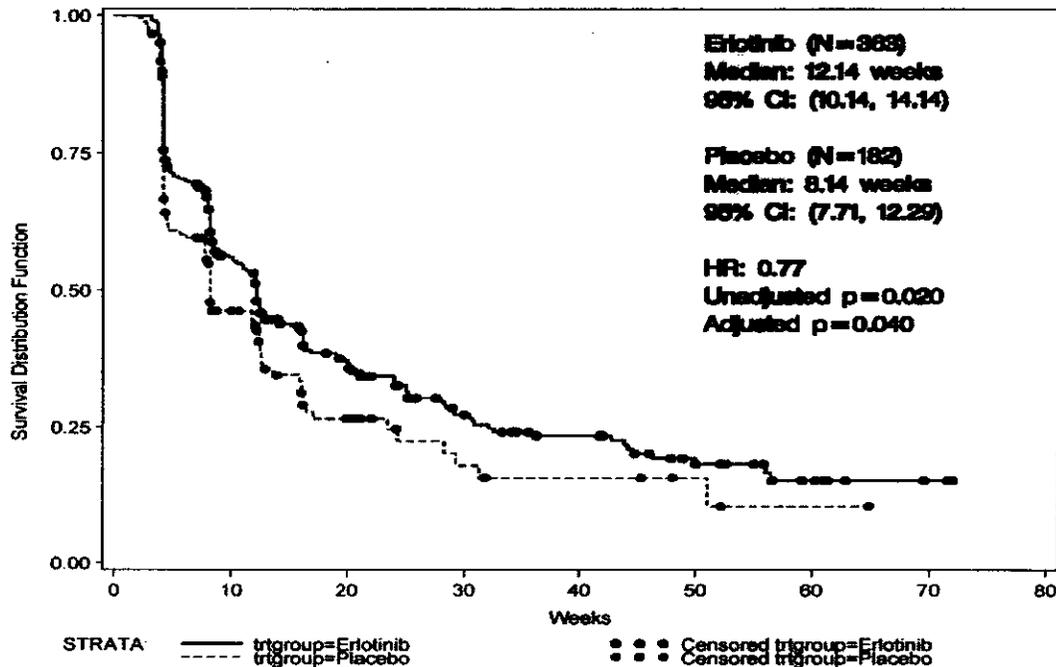


Time to Deterioration of Pain

Deterioration of pain at some time after baseline was reported for 228/363 patients in the erlotinib arm (63%) and for 113/182 patients (62%) in the placebo arm. Time to deterioration of pain is displayed in Figure 3 (Sponsor's analysis). The medians were 12.14 weeks in the erlotinib arm and 8.14 weeks in the placebo arm, unadjusted p-value = 0.020, adjusted p-value = 0.040. The HR for deterioration of pain in the erlotinib arm relative to the placebo arm was 0.77 (95% CI, 0.61-0.97).

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Figure 7: Time to Deterioration of Pain



Reviewer's Comments:

1. The statistical reviewer found that the sponsor erroneously entered one patient's "prior to randomization" data twice and, this wrong data was used to compute the time to deterioration for cough and pain symptoms. After correcting the data, this reviewer performed the re-analyses for the time to deterioration for cough and pain symptoms. It was found that only p-values had changed from 0.0417 to 0.0427 and 0.020 to 0.021 for cough and pain symptoms, respectively. Other analysis results stayed the same.
2. For the three symptoms, cough, dyspnea and pain, in addition to the time to deterioration analyses, the sponsor also constructed a pattern mixture model for each symptom to examine the impact of missing data. Since this reviewer could not verify the sponsor's analysis results due to an unclearly defined variable, the sponsor was asked to submit their program to assist in the review. In the sponsor's program, this reviewer found the sponsor had 'week' variable incorrectly calculated. Based on this reviewer's analysis results, like the sponsor's (although there was an error in the sponsor's analysis), none of the interaction terms in any of the models was statistically significant, indicating no differential effects between treatment arms caused by missing data.

3. To further examine the drug's effect on relieving lung cancer patients' symptoms on cough, dyspnea and pain, this reviewer performed an exploratory analyses using the ANCOVA model with baseline score as covariate for the change scores from baseline to Week 4 and Week 8. This analysis used LOCF (last observation carried forward) data. Table 31 summarizes the analysis results for the ANCOVA model. Although the results of these exploratory analyses by change in scores from baseline to Week 4 and Week 8 analysis suggest a trend for improvement with erlotinib, these results are not as significant as the time to deterioration analyses results for these 3 symptoms. It should be noted that time to deterioration specifically in these 3 symptoms was added later on in the statistical analysis plan (6 months after the last patient was entered on study) and was not pre-specified in the protocol.
4. For a detailed review of the choice of the questionnaire, specific questions and the 3 specific symptoms selected for the analyses, please refer to the review report by the patient reported outcome reviewer.
5. This reviewer further conducted time to deterioration analysis for other (other than cough, dyspnea and pain) symptoms/domains that were measured in QoL questionnaire. The results of these exploratory analyses are presented in Table 32 below. It is to be noted that among the 23 items listed in Table 32, 'physical functional domain', and 'global QoL scale' appear to be worse in the erlotinib group compared to placebo (HR > 1). Diarrhea and sore mouth were also significantly worse in the erlotinib arm as also evidenced by the adverse events. Furthermore, the dyspnea symptom domain was not significant. This raises doubts about the robustness of the significant findings in the time to deterioration of cough, dyspnea and pain.

Table 31: The ANCOVA model for changes from baseline to Week 4 and Week 8 (LOCF data) for Cough, Dyspnea and Pain Symptoms

Cough	Week 4		Week 8	
	Erlotinib (n=289)	Placebo (n=152)	Erlotinib (n=301)	Placebo (n=154)
Least Square Means	-3.011	2.654	-3.446	0.889
P-value	0.031		0.081	
Dyspnea	Week 4		Week 8	
	Erlotinib (n=339)	Placebo (n=174)	Erlotinib (n=356)	Placebo (n=180)
Least Square Means	-0.375	5.521	2.40	6.91
P-value	0.016		0.071	
Pain	Week 4		Week 8	
	Erlotinib (n=342)	Placebo (n=174)	Erlotinib (n=359)	Placebo (n=180)
Least Square Means	0.543	7.455	1.153	9.922
P-value	0.002		0.0002	

Table 32: Time to deterioration of symptoms except cough, dyspnea and pain

Type of Symptoms	Hazard Ratio and C.I.	p-value by log rank test
Physical Functional Domain	1.499 (1.025, 2.192)	0.0315
Role Function Domain	1.093 (0.807, 1.482)	0.5485
Emotional Functional Domain	1.169 (0.856, 1.597)	0.3086
Cognitive Functional Domain	1.026 (0.729, 1.442)	0.8802
Social Functional Domain	0.941 (0.703, 1.259)	0.6703
Fatigue Symptom Domain	0.879 (0.713, 1.084)	0.1973
Nausea/Vomiting Symptom Domain	0.948 (0.726, 1.238)	0.6895
Sleep Single Item	0.781 (0.602, 1.013)	0.0552
<i>Appetite Single Item</i>	<i>0.978 (0.774, 1.236)</i>	<i>0.8479</i>
Constipation Single Item	0.621 (0.462, 0.833)	0.0011
Diarrhea Single Item	3.391 (2.402, 4.788)	<0.0001
Global QOL Scale	1.205 (0.862, 1.686)	0.2619
<i>Hemoptysis Single Item</i>	<i>0.982 (0.656, 1.471)</i>	<i>0.9306</i>
Dyspnea Symptom Domain	0.893 (0.699, 1.142)	0.3452
Sore Mouth Single Item	1.884 (1.284, 2.763)	0.0008
Trouble Swallowing Single Item	1.051 (0.729, 1.514)	0.7863
Peripheral Neuropath Single Item	0.943 (0.677, 1.312)	0.7224
Hair Loss Single Item	1.843 (1.145, 2.967)	0.0102
Chest Pain Single Item	0.739 (0.539, 1.013)	0.0558
Shoulder Pain Single Item	0.714 (0.531, 0.959)	0.0223
Elsewhere Pain Single Item	1.108 (0.823, 1.492)	0.4875
Pain Medication Single Item	1.09 (0.717, 1.657)	0.6814

3.1.2 Study A248-1007

This study was a phase II single arm, open-label, multicenter study conducted to assess the efficacy and safety of erlotinib in patients with stage IIIB or IV, *EGFR Positive* NSCLC after failure of prior platinum-based chemotherapy. Patients received erlotinib, 150 mg daily until disease progression or unmanageable toxicity.

A total 57 patients were entered on this study with 60% females, 91% White, 77% ECOG PS 0 or 1, 74% with smoking history, and median age of 62 years. Two of the 57 had CR and 5 had PR for an objective response rate of 12.3% (95% CI: 5.1-23.7%). The median overall survival was 8.4 months (95% CI: 4.8 – 13.9 months).

Reviewer's Comment:

The results of this study are similar to the results with respect to response rate observed in Study BR.21.

3.1.3 Studies OSI2298g and BO16411

Studies OSI2298g and BO16411 were randomized, double-blinded, phase III studies of erlotinib used in combination with chemotherapy of stage IIIB or IV NSCLC chemotherapy-naïve patients. In study OSI2298g carboplatin + paclitaxel was used as the chemotherapy regimen in both treatment arms and in study BO16411 cisplatin + gemcitabine was used as the chemotherapy regimen in both treatment arms. In both the studies overall survival was the primary endpoint.

In study OSI2298g 1079 patients (539 in the erlotinib arm and 540 in the placebo arm) were enrolled. This study demonstrated that addition of erlotinib to carboplatin and paclitaxel did not improve survival compared to carboplatin + paclitaxel alone. The median survival was 324 days (95% CI: 288-381 days) in the erlotinib + chemotherapy arm compared to median survival of 319 days (95% CI: 285-344 days) in the chemotherapy alone arm.

In study BO16411 1172 patients (586 in the erlotinib arm and 586 in the placebo arm) were enrolled. This study demonstrated that addition of erlotinib to cisplatin and gemcitabine did not improve survival compared to cisplatin + gemcitabine alone. The median survival was 301 days (95% CI: 274-315 days) in the erlotinib + chemotherapy arm compared to median survival of 309 days (95% CI: 282-343 days) in the chemotherapy alone arm.

Reviewer's Comment:

Both studies provide evidence that there is no survival benefit in the addition of erlotinib to chemotherapy as treatment in chemotherapy-naïve advanced NSCLC patients. These results are similar to the results of the combination studies of irressa in this setting.

3.2 Evaluation of Safety

Please refer to Clinical Review of this application for safety evaluation.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

Efficacy by gender was analyzed by conducting exploratory survival analyses. The results of these are presented in Table 33. Efficacy by age (< 65 years vs. ≥ 65 years) was analyzed by conducting exploratory survival analyses. The results of these analyses are presented in Tables 34. Efficacy by ethnic origin with respect to overall survival is presented in Tables 35.

Table 33: Exploratory Survival Analysis by Gender

Gender	Treatment	Number of Deaths	Median Survival in Months ¹ (95% C.I.)	Hazard Ratio ² (95% C.I.)	P-value ³
Female	Placebo	70/83	6.2(4.1, 8.3)	0.797 (0.594,1.068)	0.1276
	Erlotinib	129/173	8.4 (6.5, 10.7)		
Male	Placebo	139/160	4.5 (3.6, 5.9)	0.759 (0.616,0.935)	0.0093
	Erlotinib	249/315	5.7 (4.8, 7.0)		

Table 34: Exploratory Survival Analysis by Age Group

Age Group	Treatment	Number of Deaths	Median Survival in Months ¹ (95% C.I.)	Hazard Ratio ² (95% C.I.)	P-value ³
< 65 yrs	Placebo	132/153	5.1 (4.1, 6.8)	0.752 (0.606, 0.932)	0.0090
	Erlotinib	230/299	6.1 (5.0, 7.9)		
≥ 65 yrs	Placebo	77/90	4.4 (3.5, 6.7)	0.791 (0.600, 1.043)	0.0953
	Erlotinib	148/189	7.0 (5.4, 9.0)		

¹: Kaplan-Meier Estimates; ²: Hazard Ratio of Tarceva/Placebo;

³: unadjusted log-rank test and not adjusted for multiple analyses.

Table 35: Exploratory Survival Analysis by Gender

Origin	Treatment	Number of Deaths	Median Survival in Months ¹ (95% C.I.)	Hazard Ratio ² (95% C.I.)	P-value ³
White	P	163/188	4.4 (3.5, 5.9)	0.785 (0.649, 0.950)	0.0126
	E	303/379	5.9 (4.9, 7.0)		
Oriental	P	23/28	8.4 (4.6, 10.8)	0.611 (0.365, 1.025)	0.0593
	E	40/63	13.6 (9.5, 16.2)		
Other	P	23/27	5.6 (3.7, 8.3)	0.862 (0.506, 1.467)	0.5832
	E	35/46	5.7 (3.5, 10.0)		

¹: Kaplan-Meier Estimates; ²: Hazard Ratio of E/ P; ³: unadjusted log-rank test and not adjusted for multiple analyses.

Reviewer's Comments:

1. Higher response rate was observed in females (22/173 (12.7%), 95% CI: 8.1, 18.6%) compared to males (17/315 (5.4%), 95% CI: 3.2, 8.5%) in the erlotinib treated patients. Although, erlotinib appears to improve survival in both females and males compared to placebo, the survival benefit is statistically significant in males.
2. Higher response rate was observed in younger patients (< 65 years, ORR = 28/299 (9.4%), 95% CI: 6.3, 13.3%) compared to older patients (≥ 65 years, ORR = 11/189 (5.8%), 95% CI: 2.9, 10.2%). Although, erlotinib appears to improve survival in both younger and older patients, the survival benefit is statistically significant in patients < 65 years old.
3. Higher response rate was observed in Oriental patients (10/63 (15.9%), 95% CI: 7.9, 27.3%) compared to White patients (25/379 (6.6%), 95% CI: 4.3, 9.6%) in the erlotinib treated patients. Similarly Oriental patients seem to benefit more than White patients from erlotinib compared to placebo with respect to survival.

4.2 Other Special/Subgroup Populations

Effect of erlotinib on survival was evaluated in selected subgroups based on baseline characteristics (likely prognostic factors) by conducting exploratory survival analyses. The results of these analyses are presented in Table 36.

Table 36: Treatment Comparison With Respect to Survival Within Subgroups

Subgroup	Treatment*	# of Deaths	Med. Surv. (95% CI)	HR (95% CI)	Log-rank P-value**
ECOG PS 0-1	P	134/163	6.9 (5.4, 7.8)	0.75 (0.606, 0.928)	0.0079
	E	235/326	8.0 (7.0, 10.5)		
ECOG PS 2-3	P	75/80	3.2 (2.0, 3.8)	0.752 (0.567, 0.997)	0.0466
	E	143/162	3.7 (2.7, 4.6)		
Response to prior therapy CR/PR	P	76/92	6.1 (4.3, 7.5)	0.741 (0.559, 0.982)	0.0361
	E	140/186	7.9 (6.1, 10.5)		
Response to prior therapy SD	P	71/83	6.6 (4.1, 9.0)	0.769 (0.574, 1.031)	0.0778
	E	122/166	8.2 (6.0, 10.5)		
Response to prior therapy PD	P	62/68	3.2 (2.7, 4.1)	0.785 (0.575, 1.073)	0.1267
	E	116/136	3.9 (3.0, 4.9)		
One prior therapy	P	102/122	5.5 (4.1, 7.6)	0.729 (0.571, 0.931)	0.0108
	E	185/247	6.9 (5.5, 9.0)		
Two prior therapy	P	107/121	4.4 (3.5, 5.9)	0.796 (0.628, 1.008)	0.0576
	E	193/241	6.1 (4.7, 7.8)		
Prior platinum therapy	P	194/223	4.6 (3.8, 5.6)	0.726 (0.608, 0.866)	0.0003
	E	348/449	6.5 (5.4, 7.8)		
No prior platinum therapy	P	15/20	8.0 (4.3, 16.8)	1.180 (0.634, 2.196)	0.6021
	E	30/39	8.6 (4.1, 14.1)		
Adenocarcinoma	P	99/119	5.4 (4.1, 7.8)	0.715 (0.557, 0.917)	0.0077
	E	173/246	7.8 (5.4, 10.5)		
Other Histology	P	110/124	4.3 (3.6, 5.8)	0.806 (0.639, 1.017)	0.0675
	E	205/242	6.0 (4.9, 7.2)		
Smokers	P	160/187	4.6 (3.9, 6.2)	0.865 (0.713, 1.050)	0.1410
	E	292/358	5.5 (4.7, 6.5)		
Non-smokers	P	37/42	5.6 (3.5, 8.0)	0.422 (0.278, 0.640)	< 0.0001
	E	64/104	12.3 (10.6, 16.1)		
Smokers EGFR+	P	30/35	3.8 (3.1, 6.8)	0.865 (0.530, 1.412)	0.5620
	E	46/58	9.5 (5.5, 12.1)		
Smokers EGFR-	P	27/32	5.3 (2.3, 11.6)	1.023 (0.633, 1.654)	0.9262
	E	44/53	4.1 (3.0, 6.4)		
Non-smokers EGFR+	P	11/12	3.1 (2.4, 8.3)	0.273 (0.112, 0.666)	0.0025
	E	12/18	13.6 (8.6, 20.6)		
Non-smokers EGFR-	P	3/5	12.1 (7.7, -)	1.428 (0.402, 5.076)	0.5794
	E	13/19	10.9 (4.7, 21.8)		

* P = placebo, E = erlotinib; ** not adjusted for multiplicity.

Reviewer's Comment:

These exploratory analyses suggest no apparent survival advantage with erlotinib treatment compared to placebo in the subgroups of patients: (1) who had progressive disease with prior therapy, (2) who had not received prior platinum therapy, and (3) who had smoking history.

5 Summary and Conclusions

This NDA submission is to support administration of erlotinib for patients with phase IIIB/IV advanced or metastatic non-small lung cancer. In this NDA submission, study BR.21 is the only randomized pivotal study conducted to establish efficacy and safety. This study enrolled a total of 731 patients with 488 patients who received erlotinib and 243 patients who received placebo. The primary efficacy endpoint of this study was survival. The applicant has submitted this application claiming efficacy based on overall survival. There was a statistically significant difference between the two treatment arms with respect to overall survival in the ITT population (log-rank test, P-value = 0.0018 (unadjusted analysis, P-value < 0.0001 (stratified log-rank test))).

5.1 Statistical Issues and Collective Evidence

Statistical Issues:

1. The primary analysis of the primary endpoint overall survival was based on stratified log-rank test including randomization stratification factors and EGFR status. In 67% of the patients EGFR status was not evaluated. An adjusted analysis including these 67% patients with missing data on EGFR status is questionable.
2. The results of exploratory analyses in the subgroups suggest a significant survival benefit due to erlotinib in the EGFR positive patients and suggest no survival benefit in the EGFR negative population. It is likely that the overall significant results in the ITT population are driven by the EGFR positive population. This hypothesis needs to be further evaluated.

Collective Evidence:

In this application the sponsor has submitted results of 4 studies in NSCLC patients. Two randomized studies of erlotinib in combination with chemotherapy were conducted in chemotherapy naïve advanced NSCLC patients and both the studies failed to demonstrate superior efficacy with respect to overall survival. These results are similar to the two randomized studies of iressa in combination with chemotherapy in the same patient population. The sponsor is not seeking approval in this patient setting and therefore these results are not considered as supportive evidence for the claimed benefit in second and third-line treatment of advanced NSCLC.

The sponsor has submitted supportive data from a phase II, single arm study of erlotinib conducted in *EGFR positive*, advanced, NSCLC patients. The response rate observed in this study was 12.3% (95% CI: 5.1, 23.7%). The response rate observed in the registration study BR.21 was also similar in the EGFR positive patients (10.3%; 95% CI: 4.5, 19.2%; response rate in ITT population (second and third-line patients) 8.0%, 95% CI: 5.7, 10.8%). Similar response rates were also reported for docetaxel (product label: 5.5%; 95% CI: 1.1, 15.1%; response rate reported in alimta label for docetaxel: 8.8%, 95% CI: 5.7, 12.8%) and alimta (product label: 9.1%, 95% CI: 5.9, 13.2%) in the second-line treatment for advanced NSCLC and for iressa (product label: 10.6%, 95% CI: 6.0, 16.8%) in the third-line treatment of advanced NSCLC. The response rate observed when treated with erlotinib is similar to other drugs available for the treatment of advanced NSCLC.

The median survival observed in the phase II study of erlotinib was 8.4 months (95% CI 4.8, 13.9 months). The median survival in the phase III BR.21 study which included both EGFR positive and EGFR negative patients, as well as patients requiring second and third-line of treatment, was 6.7 months (95% CI: 5.5, 7.8 months). These survival results are similar to those reported for docetaxel and alimta.

A significant survival benefit is demonstrated in the subgroup of EGFR positive patients. A significant progression-free survival and higher response rate were also observed in this subgroup with EGFR positive status.

The demonstrated survival benefit appears to be robust with significant benefit in all subgroups except in the subgroup of patients with EGFR negative status, patients with smoking history, patients who had not received prior platinum treatment and in patients who did not have a response to prior treatment regimen.

5.2 Conclusions and Recommendations

In this reviewer's opinion the study results from a single, randomized, multicenter, double-blinded, placebo-controlled phase III trial support the claim of efficacy based on overall survival of Tarceva™ (erlotinib hydrochloride) for patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

APPENDICES

Appendix 1: Measurement Schedule (Excerpt from Sponsor protocol)

Required Investigations	Prestudy	4-weekly	4 week Follow up Visit (4 weeks after off treatment)	12-Weekly
History, physical exam	X	X	X	X
Concomitant medications	X	X	X	
Clinical tumour measurement ³	X	X ²	X ³	X ⁴
ECOG PS	X	X	X	
Hemoglobin White cells, granulocytes Platelets INR ¹¹	X	X	X	
Total bilirubin Creatinine ALT LDH Total Protein Albumin	X	X	X	
CXR CT Chest ² Other scans to document all sites of disease ²	X	X ²	X ⁴	X ⁵
QoL (EORTC QLQC30 + QLQ LC13) ⁶	X	X ¹	X ⁴	X ⁴
EKG	X	X ³	X	
Pharmacokinetics / Alpha 1-acid glycoprotein (AAG) and correlative studies	X ¹⁰	X ¹⁰	X ¹⁰	
Pregnancy test	X ⁴			
Tissue block collection	X			
Graded according to CTC V2.0	X	X	X ⁷	X ⁷
<ol style="list-style-type: none"> 1. Day 1 cycle 2 and each subsequent cycle. 2. Every 8 weeks at the end of every 2 cycles. 3. Only if clinically indicated, every 8 weeks. 4. Only if WOCBP. 5. Not required after disease progression has been documented. 6. At least one Questionnaire should be completed by all patients. Patients must complete their final Questionnaire within 2 weeks of PD. Complete at 4 week visit after off treatment ONLY if not already completed within 2 weeks of PD. 7. Ongoing or new toxicity that is definitely, probably or possibly related to protocol therapy. 8. Include upper abdomen at baseline; thereafter repeat CT chest every 8 weeks, including abdomen ONLY if evidence of disease on baseline scan. If all disease visible on X-ray, CXR may be used to follow disease status. 9. Bone scans do not need to be repeated routinely except to confirm CR or PR (mandatory, positive scans only) or as clinically indicated. 10. Baseline plasma sample for PK/AAG and correlative studies. Trough sample for OSI-774 / AAG level plus plasma samples for correlative studies should be taken on day 1 of each cycle (every 4 weeks); should be taken prior to that days dose where possible. See Appendix VI and VIII. Plasma sample for correlative studies at 4 week follow up visit 11. Only for patients receiving capecitabine while on protocol therapy. To be done twice a week, weekly for 3 weeks; then weekly or more often as clinically indicated. 				

Appendix 2: Response Criteria (Excerpt from Sponsor's Protocol)

Response

All patients will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR): disappearance of all clinical and radiological evidence of tumour (both *target* and *non-target*).

Partial Response (PR): at least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.

Stable Disease (SD): steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. No new lesions.

Progressive Disease (PD): at least a 20% increase in the sum of LD of measured lesions taking as references the smallest sum LD recorded since baseline. Appearance of new lesions will also constitute progressive disease. In exceptional circumstances unequivocal progression of non-target lesions may be accepted as evidence of disease progression.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also requires
CR	CR	No	CR	≥ 4 wk. confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥ 6 wks from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

* Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented.

Stable Disease Duration

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Appendix 3: QoL Variables (excerpt from sponsor's Statistical Analysis Plan):

QLQ-C30

There are five functional domains and three symptom domains that can be derived from EORTC QLQ-C30 (see below for definitions). There are also six single items pertaining to common symptoms and one global QoL scale. If at least 50% of questions in each domain were answered, the score is calculated as for function domains:

$$\text{Score} = 100 - (((\text{Total for the answered questions} / (\text{Total questions answered})) - 1) * 100 / 3)$$

and for symptom domains, single items, and global QoL scale:

$$\text{Score} = (((\text{Total for the answered questions} / (\text{Total questions answered})) - 1) * 100 / 3)$$

Otherwise, the score will be recorded as "missing". For each single item, the score will be recorded as "missing" if the answer to this item is missing. The higher scores for function domains and global QoL scale represent better QoL while the higher scores for symptom domains and single items indicate the symptom is more severe. The following is a list of questions defining each domain, single item, and global QoL scale:

Functional Domains:

X	Physical:	Questions: 1, 2, 3, 4, 5
X	Role:	Questions: 6, 7
X	Emotional:	Questions: 21, 22, 23, 24
X	Cognitive:	Questions: 20, 25
X	Social:	Questions: 26, 27

Symptom Domains:

X	Fatigue:	Questions: 10, 12, 18
X	Nausea and vomiting:	Questions: 14, 15
X	Pain:	Questions: 9, 19

Single Items:

X	Dyspnea:	Question 8;
X	Sleep:	Question 11;
X	Appetite:	Question 13;
X	Constipation:	Question 16;
X	Diarrhea:	Question 17;
X	Financial:	Question 28.

Global QoL Scale:

X	Global QoL scale:	Questions: 29, 30
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QLQ-LC13

There are one symptom domain and 10 single items that can be derived from EORTC QLQ-LC13. The method handling missing answers to the questions and scoring algorithm are the same as that for QLQ-C30 symptom domain and single item. As before, higher scores for the symptom domain and

single items indicate the symptom is more severe. The following is the list of questions defining these domains and single items.

X	Cough:	Question: 31
X	Hemoptysis:	Question: 32
X	Dyspnea domain:	Questions: 33, 34, 35
X	Sore mouth:	Questions: 36
X	Trouble swallowing:	Questions: 37
X	Peripheral neuropathy:	Questions: 38
X	Hair loss:	Questions: 39
X	Pain in chest:	Questions: 40
X	Pain in shoulder:	Questions: 41
X	Pain elsewhere:	Questions: 42
X	Pain medication:	Questions: 43

APPEARS THIS WAY
ON ORIGINAL

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (BR.21)

We are interested in some things about you and your health. Please answer all the questions yourself by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best single response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

	Not <u>at All</u>	A <u>Little</u>	Quite <u>a Bit</u>	Very <u>Much</u>
[REDACTED]				

During the past week:	Not <u>at All</u>	A <u>Little</u>	Quite <u>a Bit</u>	Very <u>Much</u>
[REDACTED]				
[REDACTED]				
[REDACTED]				

During the past week:

Not
at All

A
Little

Quite
a Bit

Very
Much

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

For the following questions please circle the number between 1 and 7 that best applies to you.

[Redacted]

[Redacted]

APPEARS THIS WAY
ON ORIGINAL

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.

During the past week:

Not
at All A
Little Quite
a Bit Very
Much

[REDACTED]				

Please fill in your initials to indicate that you have completed this questionnaire: _____

Appendix 5: Evaluation of Baseline Prognostic Factors – Univariate Analyses

Characteristic	N	Median Survival (95% CI) in mos	HR (95% CI)	Log-rank P-value
Baseline ECOG				
0-1	489	7.6 (6.8, 8.3)	1.917	< 0.0001
2-3	242	3.3 (2.7, 4.1)	(1.619, 2.269)	
Prior Response				
CR/PR	278	7.0 (6.0, 8.0)	0.969 (0.798, 1.177) 1.563 (1.281, 1.907)	< 0.0001
SD	249	7.4 (5.8, 9.1)		
PD	204	3.5 (3.1, 4.3)		
# of Prior Regimens				
1	369	6.5 (5.4, 7.8)	1.165	0.0640
2	362	5.2 (4.5, 6.8)	(0.991, 1.370)	
Prior Platinum Tx				
Yes	672	5.7 (5.0, 6.7)	0.748	0.0615
No	59	8.2 (5.6, 12.5)	(0.551, 1.016)	
Sex				
Female	236	7.6 (6.1, 9.0)	1.193	0.0427
Male	475	5.2 (4.6, 6.1)	(1.005, 1.416)	
Age Group				
≤ 60 yrs	356	5.8 (4.7, 7.1)	1.028	0.7420
> 60 yrs	375	6.1 (5.1, 7.2)	(0.874, 1.208)	
Histology				
All other	366	5.4 (4.7, 6.3)	0.752	0.0006
Adenocarcinoma	365	7.0 (5.3, 8.2)	(0.639, 0.885)	
Smoking History				
No	146	9.9 (8.0, 11.9)	1.562	< 0.0001
Yes	545	5.1 (4.5, 6.1)	(1.258, 1.939)	

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