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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-743**

**Medical Review(s)**

**ENDPOINT**

APPLICATION TYPE	NDA
SUBMISSION NUMBER	21-743
SUBMISSION CODE	BR.21
SUBMISSION EPOCH	NDA
SUBMISSION DATE	6/22/04
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PDUFA GOAL DATE	10/1/04
REVIEWER NAME	Laurie Burke
REVIEW COMPLETION DATE	9/9/04
ESTABLISHED NAME	Erlotinib hydrochloride
(PROPOSED) TRADE NAME	Tarceva
THERAPEUTIC CLASS	NSCLC
APPLICANT	OSI Pharmaceuticals, Inc.
PRIORITY DESIGNATION	P
ENDPOINT(S) CONCEPT(S) REVIEWED	Cough, dyspnea, pain ("lung cancer related symptoms")
INSTRUMENT(S)	EORTC QLQ C30 and QLQ LC13
PRIMARY ENDPOINT(S)	Survival
FORMULATION	Oral tablet
DOSING REGIMEN	150 mg po qd until progression or toxicity
PROPOSED INDICATION	Treatment of NSCLC
INTENDED POPULATION(S)	Incurable Stage IIB/IV NSCLC with prior chemo

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## **1 INTRODUCTION AND BACKGROUND**

### **1.1 Product Information (relevant to endpoint issues)**

Erlotinib hydrochloride (Tarceva) is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor specifically inhibiting the tyrosine kinase associated with the EGFR. The EGFR or its activating ligand TGF $\alpha$  (transforming growth- factor alpha) are over-expressed in a significant percentage of tumors.

### **1.2 Proposed Indication and Supporting Endpoints**

Treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

### **1.3 Other Proposed Claims and Endpoints**

The company's proposed labeling states, t

1

### **1.4 Study Design Summary**

BR.21 is a randomized, double blind, placebo-controlled (including best supportive care) trial. This study was conducted in 17 countries, in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomized 2:1 to receive erlotinib 150 mg or placebo orally once daily until disease progression or unacceptable toxicity. Because symptom measures were considered an essential part of the study and important to the assessment of any survival gain, the patient's ability but unwillingness to complete the symptom questionnaires was a valid reason for study exclusion.

The EORTC QLQ-C30 and QLQ-LC13 were administered at baseline and on day 1 of every 4-week period on therapy, and at the 4- and 12-week post-treatment follow-up visits, if not already completed within 2 weeks of a determination of progressive disease. Site personnel completed the cover page with the date and time, location, and the reason if any questions were not answered or the patient required assistance. Patients completed the questionnaire by themselves by circling the number of the best single response per question. The form was completed during clinic visits prior to having any other evaluations or assessment of AEs. Patients were assured that the information would remain confidential.

The questionnaire was not available in Thai or Romanian languages so symptom reports in these populations were not collected. The number and reasons for patients being unevaluable were balanced by treatment arm. All patients who completed at least the baseline and one of the subsequent EORTC assessments were evaluable for the analysis of time to deterioration of cough, dyspnea and pain. 63% of erlotinib-treated patients and 64% of placebo-treated patients were evaluable for EORTC assessments. 12% in each group performed a baseline assessment only, primarily due to death. 24% and 23% in erlotinib and placebo groups respectively had no EORTC assessment at all primarily due to no translation available.

Since some patients had maximal cough, pain or dyspnea at baseline and could not possibly deteriorate, symptom deterioration analyses were repeated after excluding these patients. Median time to deterioration was still significant for each symptom according to the sponsor's analysis. An examination of concomitant meds to palliate the 3 symptoms suggested that the observed symptom benefits could not be attributed to such use.

### **1.5 Related Products**

Other EGFR tyrosine kinase inhibitors currently on the market are gefitinib (Iressa) approved for second line treatment of non-small cell lung cancer (NSCLC) and imatinib (Gleevec) approved for Philadelphia chromosome positive chronic myeloid leukemia (CML).

Another approved product with similar mechanism of action is Cetuximab (Erbix), a chimeric monoclonal antibody that inhibits the EGFR receptor through competitive binding. Cetuximab is approved for EGFR expressing metastatic colorectal cancer in combination with irinotecan (Camptosar) in patient's refractory to irinotecan-based therapy or as monotherapy in patients intolerant to irinotecan based therapy but has also been studied in NSCLC.

Early stage compounds in development include CI-1033, an irreversible pan-erbB tyrosine kinase inhibitor, and PKI166 and GM572016, both examples of dual kinase inhibitors (inhibiting epidermal growth factor receptor and Her2).

### **1.6 Relevant Product History**

Erlotinib hydrochloride (Tarceva) was granted Fast Track Designation for 2<sup>nd</sup>/3<sup>rd</sup> line NSCLC on September 5, 2002. A pre-NDA meeting was held on December 10, 2003. A rolling NDA was commenced under the FDA Pilot 1 program and a priority review was granted. The action goal date is October 1, 2004.

### **1.7 Submitted Documents Reviewed**

NDA Study BR.21

### **1.8 Other Documents Reviewed**

EORTC QLQ-C30 Manuals, Reference Values and Bibliography

## **2 ENDPOINT DOCUMENTATION SUMMARY**

The 3 lung cancer symptom endpoints are described individually below. All are measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and its lung cancer specific supplementary module (LC13).

The QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial

## ENDPOINT

impact of the disease. The QLQ-LC13 lung cancer module includes questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain). It also assesses treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and the need for pain medication.

The sponsor states that only the individual symptoms of cough, dyspnea and pain were chosen as endpoints because they are clinically relevant and frequently present in patients with advanced NSCLC. The EORTC instruments measure cough and dyspnea with single items each. Pain is measured as an average of 2 items.

“Cough” as measured by Question 1 of the QLQ-LC13 (or 31 of the combined questionnaire):  
“During the past week, how much did you cough?”

“Dyspnea” as measured by Question 8 of the QLQ-C30: “During the past week, were you short of breath?”

“Pain” as measured by Questions 9 and 19 of the QLQ-C30: “During the past week have you had pain?” and “During the past week, did pain interfere with your daily activities?”

For each item, the response options are numbered from 1 to 4 with 1 = “not at all,” 2 = “a little,” 3 = “quite a bit,” and 4 = “very much.” For each endpoint, a linear transformation was applied to standardize the raw score to range between 0 and 100. A high score represents a high level of symptomatology / problems. Transformation is accomplished according to the following formula:  $\text{Score} = \frac{\text{RS} - 1}{3} \times 100$  so that a raw score of 1 becomes 0, a raw score of 2 becomes 33, a raw score of 3 becomes 67 and a raw score of 4 becomes 100. For the pain scale, responses to the 2 questions are averaged before transformation. The possible scores are 0, 17, 33, 50, 67, 84 and 100.

Results showed that erlotinib significantly extended “time to deterioration” for each of the three symptoms scores analyzed (i.e., cough, dyspnea and pain). A patient was considered to have deteriorated for a given symptom if they exhibited a change score from baseline of 10 points or higher at any time-point after the baseline assessment. This means that any change of 1 point on the 1 to 4 scale for each item (even for the pain items that are averaged) is considered a clinically significant event in terms of deterioration.

The Hochberg procedure was used to adjust the p-values of the Log Rank tests for these 3 comparisons. No adjustment for multiplicity was applied to the overall study results.

### 2.1.1 Instrument Development, Validation and Interpretation

The EORTC initiated a research program to develop an “integrated, modular approach for evaluating the quality of life of patients participating in international clinical trials.” The EORTC QLQ-C30 was the result of that effort. Validation experience documented that the scales assess distinct components of the quality of life construct. However, no evidence was reviewed that supports the validity of the instrument to measure the individual concepts of cough, dyspnea and pain.

The EORTC QLQ-C30 scoring manual suggests that it is often advisable to report the raw scores in addition to the transformed scores (to the 0-100 scale) since it may be clinically relevant to know the proportion of patients that answer "quite a bit" or "very much." They also suggest that it may be useful to dichotomise scores, for example, by grouping scores into "not at all" versus other.

The scoring manual also reports on work by Osoba et al. who developed the Subjective Significance Questionnaire (SSQ) that asks patients about perceived changes using a 7-point scale ranging from "much worse" to "much better." Patients who reported "a little" change for better or worse on a particular symptom scale had QLQ-C30 changes about 5 to 10. Those reporting "moderate" change had changed about 10 to 20, and "very much" change corresponded to a change greater than 20. The reference did not give correlations of the SSQ with specific scales of the QLQ-C30.

### **3 REVIEW**

#### **3.1 General Comments**

The EORTC-QLQ-C30 is the most commonly used "quality of life" instrument in European cancer trials.

The symptom questions used as endpoints in this NDA are components of the EORTC QLQC30. The questions ask patients to average their experience over the past week. We don't know how patients do this. If they are having a bad day in terms of a particular symptom on the day they answer the question, they probably won't have the same answer as if their bad day was 5 days ago. In general, we prefer static assessments that ask patients about their current state rather than ask questions that require the patients to average their experience over a period of time.

Deterioration in each symptom is defined as a decrement by 1 point on any of the items analyzed. This is the smallest change score possible with this scale, but each item has only 4 response options (range of 1 to 4) so that a change of 1 can represent a substantial amount of change. In addition, there is no information available to cause us to have confidence that a decrement of 1 point at the top of the scale ("quite a bit" to "very much") means the same thing in terms of deterioration as a decrement at the lower end of the scale ("not at all" to "a little").

#### **3.2 Cough as measured by Question 1 of the QLQ-LC13**

During the past week, how much did you cough? (Response options: not at all, a little, quite a bit, very much)

We have seen other measures of cough that ask patients to qualify the cough in terms of its severity, productivity or its impact on functioning. If this single item is used to support claims in labeling, care must be taken to ensure that those other aspects of cough are not implied and that only the "amount of coughing" was used as an indicator of deterioration.

#### **3.3 Dyspnea as measured by Question 8 of the QLQ-C30**

"During the past week, were you short of breath?" (Response options: not at all, a little, quite a bit, very much)

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There has been a lot of discussion about measurement of the concept of "dyspnea" in the CDER in the area of COPD. Dyspnea has been described as having more than a single component since shortness of breath is directly related to the magnitude of effort and the magnitude of the task at the time of the shortness of breath assessment. For example, questionnaires have tried to characterize dyspnea in terms of whether difficulty with breathing occurred during strenuous activity, during light activity, during basic activities of daily living or during rest. Simply asking a patient whether they were short of breath without the context of the activity that precipitated the shortness of breath is less informative. This non-standardized format could be acceptable in a study designed to show an improvement in dyspnea, but when the endpoint is time to deterioration, we could be attributing a treatment effect to the results when in fact patients are accommodating to lower levels of activity. If this accommodation is not measured, we have no way of knowing whether this is happening differently between treatment arms.

### 3.4 Pain as measured by Questions 9 and 19 of the QLQ-C30

"During the past week have you had pain?" and "During the past week, did pain interfere with your daily activities?" (Response options: not at all, a little, quite a bit, very much)

Question 9 asks whether a patient has experienced any pain without any indication of the intensity of the pain. Question 19 asks about the impact of pain on functioning. Responses to these 2 items are averaged. A change could therefore be the result of a worsening in the reported frequency of pain or in the reported interference that pain had on functioning. Both of these responses are dependent on other important but unmeasured events such as the amount of pain meds used and the amount of activity attempted. The results reported are therefore not conclusive about the actual impact of treatment on the rate of deterioration in the patient's condition with respect to pain.

## 4 RECOMMENDATION ON REGULATORY ACTION

The measures of these 3 concepts (cough, dyspnea and pain) are not consistent with the agency's previous experience and advice for patient-reported measures. Interpretation of the meaning of these measures is problematic. We discourage the use of these measures to support claims in labeling.

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5 APPENDICES

5.1 EORTC QLQ30 and LC13



EORTC QLQ-C30 (version 2.0.)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:  
 Your birthdate (Day, Month, Year):  
 Today's date (Day, Month, Year):


	No	Yes
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2. Do you have any trouble taking a long walk?	1	2
3. Do you have any trouble taking a short walk outside your home?	1	2
4. Do you have to stay in a bed or a chair for most of the day?	1	2
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2

During the past week:

	Not at all	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you feel tired?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:

	Not at all	A little	Quite a bit	Very much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

29. How would you rate your overall physical condition during the past week?

1      2      3      4      5      6      7  
 Very poor      Excellent

30. How would you rate your overall quality of life during the past week?

1      2      3      4      5      6      7  
 Very poor      Excellent



EORTC QLQ-LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	A bit	Very much
1. How much did you cough?	1	2	3	4
2. Did you cough blood?	1	2	3	4
3. Were you short of breath when you rested?	1	2	3	4
4. Were you short of breath when you walked?	1	2	3	4
5. Were you short of breath when you climbed stairs?	1	2	3	4
6. Have you had a sore mouth or tongue?	1	2	3	4
7. Have you had trouble swallowing?	1	2	3	4
8. Have you had tingling hands or feet?	1	2	3	4
9. Have you had hair loss?	1	2	3	4
10. Have you had pain in your chest?	1	2	3	4
11. Have you had pain in your arm or shoulder?	1	2	3	4
12. Have you had pain in other parts of your body?	1	2	3	4

If you have pain, did it help?

13. Did you take any medicine for pain?	Yes	No		
If yes, did it help?	1	2	3	4

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# **Clinical Review**

<b>Application #</b>	<b>NDA 21-743</b>
<b>Drug Name</b>	<b>Tarceva (erlotinib HCl)</b>
<b>Medical Reviewer</b>	<b>Martin H. Cohen, M.D.</b>
<b>Medical Team Leader</b>	<b>John R Johnson, M.D.</b>
<b>Documents reviewed</b>	<b>\\CDSESUB1\N21743\N_000</b> <b>2004-06-22</b> <b>2004-06-28</b> <b>2004-07-07</b> <b>2004-07-29</b> <b>2004-08-03</b> <b>2004-08-06</b> <b>2004-08-18</b> <b>2004-08-20</b> <b>2004-08-30</b> <b>2004-09-01</b> <b>2004-09-02</b>

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## Clinical Review for NDA 21-743

### Executive Summary

#### **I. Recommendations**

##### **A. Recommendation on Approvability**

The clinical reviewer of the Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA recommends regular approval of NDA 21-743 (Erlotinib, OSI-774, Tarceva™). Tarceva is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

Erlotinib (OSI-774, Tarceva™) as second- and third-line therapy for advanced/metastatic NSCLC, 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. Erlotinib also demonstrated favorable effects on response rate (8.9% versus 0.9%) and on progression free survival (9.86 weeks versus 7.86 weeks). The major drug-related adverse events of erlotinib were rash and diarrhea, which were of mild to moderate intensity (NCI-CTC Grade 1 or 2) in the majority of affected patients.

Of concern is whether these results apply only to EGFR positive patients. Study patients with EGFR-positive tumors seem to derive more survival benefit than patients with EGFR-negative tumors (10.7 months versus 5.2 months). The problem is that pathology blocks or slides to determine EGFR expression status (DAKO EGFR pharmDx™ kit) were available and the results were interpretable only for 31% of the patients in the erlotinib arm and for 35% of the patients in the placebo arm.

The small numbers of patients with evaluable EGFR expression status produce estimates of hazard ratios (HR) with wide confidence intervals (CI). For example, although the HR among EGFR-negative patients is 1.01, the lower bound of the 95% CI is 0.65, which is the point estimate of the HR among EGFR-positive patients. The 95% CIs for these two subsets are overlapping. Further, there appear to be differences in prognostic factors among EGFR positive and negative patients suggesting that EGFR may be a favorable prognostic marker in NSCLC, similar to a positive estrogen receptor status in breast cancer,

It is of importance to obtain additional data to resolve this question. Because interpretable immunohistochemical EGFR expression results will be available only for approximately 40 additional patients in study BR.21 it is unlikely that the EGFR question can be answered at this time. The sponsor will be asked to collect EGFR status

data for patients who have received, or will receive erlotinib in ongoing and future studies.

#### **B. Recommendation on Phase 4 Studies and/or Risk Management Steps**

The sponsor will be required to obtain pathology blocks to determine EGFR status in the current study, BR.21, and in future studies.

## **II. Summary of Clinical Findings**

### **A. Brief Overview of Clinical Program**

A single double-blind trial titled "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" Protocol Number BR.21 was submitted. The study was performed by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). Patients with advanced or metastatic non-small cell lung cancer (NSCLC) (Stage IIIB/IV) who have failed at least one but not more than two prior regimens were randomized 2:1 to receive erlotinib 150 mg orally once per day or placebo. Study drug administration was continued until disease progression or unacceptable toxicity. The treatment arms were compared for overall survival, response, progression-free survival, quality of life, and safety. The first patient was randomized 01 Nov 2001, the last patient was randomized 31 Jan 2003. The study is closed to enrollment, 28 patients are still on-study. The data base lock was 23 April 2004.

### **B. Efficacy**

Erlotinib (OSI-774, Tarceva™) as second- and third-line therapy for advanced/metastatic NSCLC, 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. Erlotinib also demonstrated favorable effects on response rate (8.9% versus 0.9%) and on progression free survival (9.9 weeks versus 7.9 weeks).

### **C. Safety**

Erlotinib therapy was generally well tolerated. The most frequently occurring toxicities were skin rash and diarrhea, generally CTC grades I and II. These toxicities only occasionally resulted in dose-reduction or discontinuation of treatment. Other gastrointestinal symptoms included anorexia, nausea and vomiting, again generally mild. No new or unexpected safety findings emerged from this placebo-controlled study. Despite a very extensive attempt to identify possible pulmonary toxicity such as interstitial pneumonitis, no difference between the treatment arms was apparent. Patients receiving concurrent warfarin treatment had INR values outside the normal range (26%

## CLINICAL REVIEW

in the erlotinib arm vs 21% in the placebo arm). Hematology and chemistry toxicity was mild.

### **D. Dosing**

The recommended daily dose of Erlotinib is 150 mg taken at least one hour before or two hours after the ingestion of food

### **E. Special Populations**

**Pediatrics** - The safety and effectiveness of Erlotinib in pediatric patients have not been studied.

**Elderly** - Of the total number of patients participating in trial BR.21, 62% were less than 65 years of age, and 38% of patients were aged 65 years or older. The survival benefit was maintained across both age groups. No meaningful differences in safety or pharmacokinetics were observed between younger and older patients. Therefore, no dosage adjustments are recommended in elderly patients.

**Gender** - The survival benefit of Erlotinib was similar in males and females. No gender effect on safety was observed.

**Race/Ethnicity** - There was no significant effect of race/ethnicity on either efficacy or safety results.

**Renal or Hepatic Impairment** - Erlotinib and its metabolites are not significantly excreted by the kidneys. Less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

Erlotinib is predominately cleared by the liver. No data are currently available regarding the influence of hepatic dysfunction and/or hepatic metastases on the pharmacokinetics or safety of Erlotinib.

### **Pregnancy - Category**

Erlotinib has been shown to cause maternal toxicity with associated embryo/fetal lethality and abortion in rabbits when given at doses that result in plasma drug concentrations of approximately 4 times those in humans (based on AUCs observed at a daily dose of 150 mg). At plasma drug concentrations of 1-2 times those in humans, there was no increased incidence of embryo/fetal lethality or abortion in rabbits or rats.

No teratogenic effects were observed in rabbits or rats.

There are no adequate and well-controlled studies in pregnant women using erlotinib. Women of childbearing potential must be advised to avoid pregnancy while on erlotinib. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus. If erlotinib is used during

pregnancy, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

**Nursing Mothers**

It is not known whether erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of erlotinib on infants have not been studied, women should be advised against breast-feeding while receiving erlotinib therapy.

***Clinical Review***

**I. Introduction and Background**

**A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups**

**Proposed name:** Tarceva

**Proprietary Name:** Erlotinib (USAN) (Erlotinib [INN], OSI-774,)

**Applicant:** OSI Pharmaceuticals, Inc.

**Drug Class:** Targeted EGFR antagonist

**Current Indication:** None

**Proposed Indication:** Erlotinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

**Dosage and Administration:** The recommended daily dose of erlotinib is 150 mg taken at least one hour before or two hours after the ingestion of food.

**B. State of Armamentarium for Indication(s)**

Prior to the 1980s available chemotherapy drugs demonstrated limited activity against NSCLC. In the 1980s, several agents were introduced, including cisplatin, mitomycin C, ifosfamide, vindesine, vinblastine, carboplatin, and etoposide. Response rates of these drugs as single agents ranged from 10% to 20%, with

combinations resulting in response rates of 20% to 40%. Median survival times ranged between 5 months to 10.8 months.

Vinorelbine is approved for first-line treatment of advanced NSCLC in several countries, including US, France, Italy, Spain, Germany, and UK, both as a single agent and in combination with cisplatin. As a single agent, it has shown response rates of 20% or higher. The combination of vinorelbine and cisplatin has, in some studies, resulted in improved response rates and survival advantages compared to either agent alone, with 1-year survival rates of 33% to 35% compared to 12% for cisplatin and 30% for vinorelbine. One study of vinorelbine plus cisplatin versus vinorelbine alone showed a higher response rate for the combination (43% versus 16%), but no advantage in median survival time (33 weeks for vinorelbine plus cisplatin versus 32 weeks for vinorelbine alone).

Gemcitabine and paclitaxel were both approved in 1998 in the US for use in combination with cisplatin for the first-line treatment of advanced NSCLC. In five Phase 2 trials of the gemcitabine/cisplatin combination, response rates ranged from 38% to 54% and median survival from 8.4 months to 14.3 months. In a Phase 3 study of paclitaxel combined with cisplatin, without and with filgrastim, response rates were 27% and 32%, and median survival times were 9.5 and 10.5 months, respectively.

Docetaxel combination with cisplatin was approved in 2002, for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition. Docetaxel was assessed in a single, open-label multicenter international randomized controlled trial. A total of 1218 patients with unresectable stage IIIB or IV NSCLC, Karnofsky performance status 70 to 100 and no prior chemotherapy were randomized.

The primary endpoint was overall survival. There was no statistically significant difference in overall survival between patients receiving docetaxel + cisplatin compared to patients receiving vinorelbine + cisplatin (median survival 10.9 months versus 10.0 months,  $p=0.12$ ). The efficacy of docetaxel in this combination was established by a non-inferiority analysis.

Historically, NSCLC has not responded well to second-line chemotherapy. In December 1999, however, docetaxel was approved in US for use in patients with locally advanced or metastatic NSCLC after failure of prior platinum-containing chemotherapy.

In May 2003 gefitinib (Iressa™, AstraZeneca Pharmaceuticals LP) received accelerated approval as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies. Objective response rate and response duration were efficacy surrogates supporting approval. In the first-line treatment of NSCLC, two large,

controlled, randomized trials showed no benefit from adding gefitinib to doublet, platinum-based chemotherapy. Therefore, gefitinib is not indicated for use in this setting.

**C. Important Milestones in Product Development**

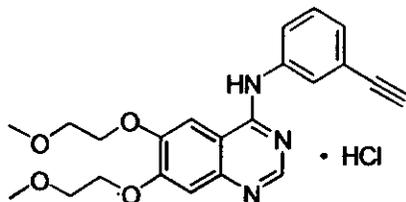
Erlotinib was discovered by OSI Pharmaceuticals, Inc. (OSI, originally Oncogene Sciences) in the early 1990s, as part of a research collaboration with Pfizer, Inc. The initial non-clinical pharmacology, pharmacokinetic, and toxicology studies were conducted by Pfizer. Pfizer initiated the clinical development program in 1995 with Phase I trials in healthy subjects followed by Phase I and II trials in patients with advanced solid tumors. Pfizer was required to divest erlotinib as a result of the acquisition of Warner Lambert in 1999 and the pharmaceutical development program was transferred to the sponsorship of OSI in June 2000. OSI subsequently entered into a co-development agreement with Genentech, Inc., and F. Hoffmann-La Roche, Ltd. As a result, the development program contains clinical data and clinical study reports generated by Pfizer, OSI, Genentech, and Roche.

The initial Erlotinib EOP2 meeting was held on 11/21/02. Follow-ups were on 9/11/02, 10/10/02, 11/13/02 and 2/13/03. Erlotinib was given fast track status in August 2002. A pre-NDA meeting was held on July 21, 2003 and December 8, 2003. No SPA was submitted. The application was initiated as a rolling NDA on January 20, 2004, with the filing of the complete CMC and Non-clinical Sections, and the associated Module 2 summaries/overview. These Sections were filed as RU#1 and RU#2, respectively. However on June 24, this NDA was accepted onto the FDA's Pilot 1 program and these units were renamed RUC-001 and RUP-002, respectively. The final clinical overview and clinical summary were submitted on July 29, 2004.

**D. Other Relevant Information**

TARCEVA (Erlotinib hydrochloride) is a human epidermal growth factor receptor type 1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor. Erlotinib, the active ingredient of TARCEVA, is a quinazolinamine with the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine. Erlotinib hydrochloride has the following structural formula:

**Figure 1: Erlotinib structure**



Erlotinib hydrochloride has the molecular formula  $C_{22}H_{23}N_3O_4 \cdot HCl$  and a molecular mass of 429.90.

Erlotinib tablets are available in three dosage strengths containing erlotinib hydrochloride equivalent to 25 mg, 100 mg or 150 mg of erlotinib and the following inactive ingredients: lactose monohydrate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The tablets also contain trace amounts of color additives including FD&C Yellow #6 (25 mg only) for product identification.

### **Drug Interactions**

Substances that are potent inhibitors of CYP3A4 activity (e.g. ketoconazole) decrease erlotinib metabolism and increase erlotinib plasma concentrations. Therefore, caution should be used when administering or taking CYP3A4 inhibitors with erlotinib.

Substances that are potent inducers of CYP3A4 activity (e.g. rifampicin) increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

### **International Normalized Ratio Elevations**

International Normalized Ratio (INR) elevations, and infrequent reports of bleeding events including gastrointestinal bleeding have been reported in clinical studies, some associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

### **E. Important Issues with Pharmacologically Related Agents**

None

## **II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews**

### **Clinical Pharmacology and Biopharmaceutics**

Orally administered erlotinib is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at approximately 4 hrs after oral dosing. A study in normal healthy volunteers provided an estimated oral bioavailability of 59%. The exposure after an oral dose may be increased by food.

Following absorption, erlotinib is highly bound in blood, with approximately 95% bound to blood components, primarily to plasma proteins (i.e. albumin and alpha-1 acid glycoprotein concentrations (AAG)).

Erlotinib has a mean apparent volume of distribution of 232 liters and distributes into tumor tissue of humans. In a study of 4 patients (3 with non-small-cell lung cancer and 1 with laryngeal cancer) receiving 150 mg daily oral doses of erlotinib, tumor samples from surgical excisions on Day 9 of treatment revealed tumor concentrations of erlotinib that ranged from 144 to 2083 ng/gm (mean 1,185 ng/gm) of tissue. This corresponded to an overall average of 63% (5% to 160%) of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumor at concentrations averaging 160 ng/gm tissue, which corresponded to an overall average of 113% (88% to 130%) of the observed steady state peak plasma concentrations. Tissue distribution studies using whole body autoradiography following oral administration with [<sup>14</sup>C] labeled erlotinib in athymic nude mice with HN5 tumor xenografts have shown rapid and extensive tissue distribution.

**Metabolism and Elimination:**

Erlotinib is metabolized in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2, and the pulmonary isoform CYP1A1. *In vitro* studies indicate approximately 80-95% of erlotinib metabolism is by the CYP3A4 enzyme. There are three main metabolic pathways identified: 1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids; 2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in preclinical *in vitro* assays and *in vivo* tumor models. They are present in plasma at levels that are <10% of erlotinib and display similar pharmacokinetics as erlotinib. The metabolites and trace amounts of erlotinib are excreted predominantly via the feces (> 90%), with renal elimination accounting for only a small amount of an oral dose.

**Exposure:**

Following a 150 mg oral dose of erlotinib, at steady state, the median time to reach maximum plasma concentrations is approximately 4.0 hours with mean maximum plasma concentrations achieved of 1,995 ng/mL. Prior to the next dose at 24 hours, the mean minimum plasma concentrations are 1,238 ng/mL. Mean AUC achieved during the dosing interval at steady state are 41,300 ng\*h/mL.

**A. Statistics**

See statistical review

**B. Chemistry**

See chemistry review.

**C. Animal Pharmacology and Toxicology**

See animal pharmacology and toxicology review.

### **III. Human Pharmacokinetics and Pharmacodynamics**

#### **A. Pharmacokinetics**

Erlotinib and its metabolites are not significantly excreted by the kidneys. Less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

Erlotinib is predominately cleared by the liver. No data are currently available regarding the influence of hepatic dysfunction and/or hepatic metastases on the pharmacokinetics or safety of Erlotinib.

#### **B. Pharmacodynamics**

A population pharmacokinetic analysis in 591 patients receiving single agent erlotinib shows a mean apparent clearance of 4.47 L/hour with a median half-life of 36.2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7-8 days. No significant relationships between predicted apparent clearance and patient age, body weight, gender, and ethnicity were observed.

Patient factors, which correlate with erlotinib pharmacokinetics, are serum total bilirubin, AAG, and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a slower rate of erlotinib clearance; however, smokers had a higher rate of erlotinib clearance.

### **IV. Description of Clinical Data and Sources**

#### **A. Overall Data**

Electronic databases provided by the sponsor were analyzed to independently confirm the sponsor's efficacy and safety results. Queries were sent to the sponsor to clarify issues that arose during the review. Any discrepancies between reviewer and sponsor were communicated to the sponsor to achieve mutually acceptable conclusions.

## CLINICAL REVIEW

### Listing of Submitted Clinical Trials

Study Identifier	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration; Duration of Erlotinib Treatment.	Number of Subjects or Patients	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
<b>Controlled Clinical Studies Pertinent to the Claimed Indication</b>						
BR.21 Phase III	Efficacy and safety in advanced refractory NSCLC; Population PK analysis	Randomized, double-blind, placebo-controlled	Erlotinib/placebo 2:1 ratio 150 mg PO QD; continuous daily dosing	485 erlotinib 242 placebo	Advanced NSCLC	Complete; Full
<b>Uncontrolled Clinical Studies Pertinent to the Claimed Indication</b>						
A248-1007 Phase II	Efficacy and safety in advanced NSCLC; Population PK analysis	Open-label	Erlotinib 150 mg PO QD; Continuous daily dosing	57	NSCLC	Complete; Full
<b>Other Clinical Studies</b>						
<b>Controlled Studies: Other Indications</b>						
OSI2298g Phase III	Efficacy and safety in first-line advanced NSCLC; Population PK analysis	Randomized, double-blind, placebo-controlled	Erlotinib/placebo 150 mg PO QD + paclitaxel 200 mg/m <sup>2</sup> IV and carboplatin AUC 6 IV Day 1 q21d for up to 6 cycles; Continuous daily dosing	526 erlotinib 533 placebo	NSCLC	Complete; Full
BO16411 Phase III	Efficacy and safety in first-line advanced NSCLC; Population PK analysis	Randomized, double-blind, placebo-controlled	Erlotinib/placebo 150 mg PO QD + gemcitabine 1250 mg/m <sup>2</sup> on Days 1, 8 q21d + cisplatin 80 mg/m <sup>2</sup> on Day 1 q21d for up to 6 cycles; Continuous daily dosing	580 erlotinib 579 placebo	NSCLC	Complete; Full
<b>Uncontrolled Studies: Other Indications</b>						
A248-101 Phase II	Efficacy and safety in ovarian cancer	Open-label	Erlotinib 150 mg QD; Continuous daily dosing	34	Ovarian cancer	Complete; Full
A248-1003 Phase II	Efficacy and safety in head and neck cancer	Open-label	Erlotinib 150 mg QD; Continuous daily dosing	115	Head and neck cancer	Complete; Full

## CLINICAL REVIEW

OSI2288g Phase II	Efficacy and safety in metastatic breast cancer	Open-label	Erlotinib 150 mg QD	68	Breast cancer	Complete; Full
OSI-774-DMS- Phase II	Evaluate effect on EGFR- with advanced EGFR+ tumors	Open-label	Erlotinib 150 mg QD for Continuous daily dose	4	Aerodigestive EGFR+ tumors	Complete; Synopsis
OSI-774-151 Phase Ib	Safety and Efficacy in combination with docetaxel in advanced solid tumors; PK analysis	Open-label	Erlotinib 100, 125 or 150 mg QD with docetaxel 60- and 75 mg/m <sup>2</sup> IV on D1 q21d; Continuous daily dosing	26	Advanced solids tumors	Complete; Synopsis
OSI-774-152 Phase Ib	Safety and Efficacy in combination with capecitabine in advanced solid tumors; PK analysis	Open-label	Erlotinib 75, 100 or 150 mg QD with capecitabine 2000 mg/m <sup>2</sup> PO × 14d q21d; Continuous daily dosing	21	Advanced solid tumors	Complete; Synopsis
OSI-774-153 Phase Ib	Safety and Efficacy in combination with paclitaxel/carboplatin in newly diagnosed or minimally pretreated malignancies; PK analysis	Open-label	Erlotinib 100, 125 or 150 mg QD with paclitaxel 225 mg/m <sup>2</sup> IV on D1 q21d and carboplatin IV AUC 6 mg·min/ml on D1 q21d; Continuous daily dosing	20	Untreated or minimally pretreated malignancies	Complete; Synopsis
OSI-774-154 Phase Ib	Safety and Efficacy in combination with gemcitabine/cisplatin in newly diagnosed or minimally pretreated malignancies; PK analysis	Open-label	Erlotinib 100 or 150 mg QD with gemcitabine 1000- or 1250 mg/m <sup>2</sup> IV on D1 and D8 q21d and cisplatin 60 or 100 mg/m <sup>2</sup> IV on D1 q21d; Continuous daily dosing	25	Untreated or minimally pretreated malignancies	Complete; Synopsis

**A. Postmarketing Experience**

None.

**B. Literature Review**

Submitted phase 2 and phase 3 published trials were reviewed.

**V. Clinical Review Methods**

**A. How the Review was Conducted**

The efficacy review is based primarily on analysis of data submitted as SAS transport files for one multicenter double-blind trial (Protocol Number: BR.21) titled "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".

Tumor evaluation for both measurable and non-measurable lesions were provided in the Tumor Assessment database. Reported dates of progression that were not supported by tumor measurements or by the occurrence of new lesions were not accepted. Patients who had not progressed were censored on the last date that a full assessment for progression was performed.

If there was a disagreement between the FDA reviewer and OSI as to response status or in the date of progression or censoring the patient was reviewed again by both the sponsor and the FDA. Correspondence regarding these reviews occurred on several occasions. All disputes were satisfactorily resolved.

**B. Overview of Materials Consulted in Review**

See above.

**C. Overview of Methods Used to Evaluate Data Quality and Integrity**

DSI on-site audit was used to audit sponsors data quality, integrity and analysis

**D. Were Trials Conducted in Accordance with Accepted Ethical Standards**

Yes

**E. Evaluation of Financial Disclosure**

Study investigators were requested to disclose any proprietary interest in OSI-774 (Tarceva™) or a significant equity in the SPONSOR/OSI as defined in 21 CFR

54.2(b) and they disclosed no such interests. In light of the co-development partnership between OSI, Genentech and Roche (the Tripartite), the active investigators were subsequently asked to re-certify that they had no financial interest in any of the three companies. No clinical investigator in Study BR.21 declared a financial interest.

## **VI. Integrated Review of Efficacy**

### **A. Brief Statement of Conclusions**

Study BR.21 was a pivotal Phase III study conducted in patients with Stage IIIB/IV NSCLC after failure of at least 1 standard chemotherapy regimen. Patients enrolled in this study were treated once daily with doses of 150 mg of erlotinib or equivalent placebo. Erlotinib provided a statistically significant prolongation of survival (median survival (6.67 months erlotinib vs 4.70 months placebo, HR = 0.73,  $p < 0.001$ ) and progression-free survival (median PFS 9.9 weeks versus 7.9 weeks). A favorable erlotinib treatment effect was demonstrated in all secondary endpoints, including response rate and time to deterioration of lung cancer symptoms (cough, dyspnea and pain).

### **B. General Approach to Review of the Efficacy of the Drug**

Individual patient data provided electronically by the sponsor were analyzed to confirm sponsor's reported results and analyses.

### **C. Detailed Review of Trials by Indication**

The efficacy review is based primarily on one multicenter, double-blind, trial titled "Randomized Placebo-Controlled Study of OSI-774 (Tarceva<sup>TM</sup>) in Patients With Incurable Stage IIIB/IV Non-Small Cell Lung Cancer Who Have Failed Standard Therapy For Advanced or Metastatic Disease".

#### **1. Protocol Review**

The phase 3 study protocol (BR.21) and the amendments to the protocol are provided in the appendix.

Table 1 lists the study investigators of trial BR.21

## CLINICAL REVIEW

**Table 1: Study investigators**

Site Code	Site Number	Investigator	Institution/Address/Phone	No. Patients Randomized
ARAI	515	Daniel Campos, MD	Centro Medico Confidence Chacabuco 469 San Isidro Buenos Aires CP 1642 Argentina 54 11 4743 2868	22
ARAK	516	Elizabeth Mickiewicz, MD/	Instituto Oncologico Angel Roffo Av San Martin 5481 Capital Federal Buenos Aires CP 1417 Argentina 54 11 4580 2808 ext 25	6
ARAL	517	Justina Lady Martinez, MD	Hospital Britanico Av. Cordoba 966, 1° P°- 1054 Buenos Aires Perdriel 74-1280 Buenos Aires Argentina 54 11 4309 6400	7
ARAM	518	Mirta Varela, MD	Hospital Italiano de Buenos Aires Gascon 450 Capital Federal Buenos Aires CP 1181 Argentina 54 11 4958 1351	6
ARAN	519	Maximiliano van Kooten, MD	Instituto Alexander Fleming Cramer 1180 Capital Federal Buenos Aires CP 1426 Argentina 54 11 6323 2900	16
ARAO	520	Mario Freue, MD	Hospital Interzonal de Agudos Evita Rio de Janeiro 1910 Lanus Buenos Aires CP 1824 Argentina 54 11 4241 5189	5
ARAQ	521	Silvia Jovtis, MD	Hospital Churruca Visca Uspallata 3400 Capital Federal Buenos Aires CP 1437 Argentina 54 11 4919 4100	3
AUAA	100	Danny Rischin, MD	Peter MacCallum Cancer Institute Department of Haematology and Medical Oncology St. Andrews Place East Melbourne VIC 3002 Australia 61 3 9656 1804	0
AUAB	101	Mark Rosenthal, MD	The Royal Melbourne Hospital Dept of Oncology Grattan Street Parkville VIC 3050 Australia 61 3 9342 7560	6
AUAF	501	Michael Byrne, MD	Sir Charles Gairdner Hospital Department of Medical Oncology Hospital Avenue Nedlands WA 6009 Australia 61 8 9346 3841	3
AUGA	492	Desmond Yip, MD	The Canberra Hospital Medical Oncology Yamba Drive Garran ACT 2605 Australia 61 2 6244 2220	7
AUGD	548	Richard deBoer, MD	Western Hospital Oncology Research Gordon Street Footscray VIC 3011 Australia 61 3 8345 6666	5
AUHW	497	Shane White, MD	Austin and Repatriation Medical Centre Studley Road Heidelberg VIC 3084 Australia 61 3 9387 1000	0
AUNS	505	Stephen Ackland, MD	Newcastle Mater Hospital Department of Medical Oncology Locked Bag 7 HRMC Waratah NSW 2310 Australia	1
AURA	493	Craig Lewis, MD	Prince of Wales Hospital Department of Medical Oncology High Street Randwick NSW 2031 Australia 61 2 9382 2585	0
AURP	552	Philip Clingan, MD	Southern Medical Day Care Centre 410 Crown Street Wollongong NSW 2550 Australia 61 2 4228 6200	6
AUWA	356	Ian Olver, MD	Royal Adelaide Hospital Royal Adelaide Hospital Cancer Centre Department of Medical Oncology North Terrace Adelaide SA 5000 Australia 61 8 8222 5577	0
BRBE	506	Auro del Giglio, MD	Faculdade de Medicina do ABC Oncologia - anexo 3 Av Principe do Gales, 821 Santo Andre SP CEP 09060-650 Brazil 55 11 4993 5491	7
BRBI	498	Clarissa Mathias, MD	Nucleo de Oncologia da Bahia R Baependi 102-Ondina Salvador BA 40170-070 Brazil 55 71 331 8198, ext. 28	6
BRBL	484	Ilka Lopes Santoro, MD	Escola Paulista de Medicina Universidade Federal de Sao Paulo Ambulatorio de Quimioterapia de Adultos Rua Pedro do Toledo, 715 Sao Paulo SP CEP 040039-03 Brazil	2
BRBM	494	Andre Marcio Murad, MD	Hospital Vera Cruz S/A Instituto de Oncologia Rua Paracatu, 759 Belo Horizonte, MG CEP 30190-130 Brazil	5
BRCE	499	Ronaldo de Albuquerque Ribeiro, MD	Instituto do Cancer do Ceara, Oncologia Clinica R Papio Jr, 1222, 5 andar Rodolfo Teofilo Fortaleza CE CEP 60430-230 Brazil 55 85 288 4527 or 4542	12

**CLINICAL REVIEW**

Site Code	Site Number	Investigator	Institution/Address/Phone	No. Patients Randomized
BRPL	495	Jose Rodrigues Pereira, MD	Instituto do Cancer Arnaldo Vieira de Carvalho R. Dr. Cesario Motta Jr., 112 San Paulo SP 01221-020 Brazil 55 11 222 7877	92
BRRD	512	Sergio Lago, MD	Centro Clinico da PUC Av. Ipiranga 6690 - sala 228, Porto Alegre RS CEP 90610-000 Brazil 55 51 3320 3319	12
BRRH	522	Jeferson Jose da Fonseca Vinholes, MD	Irmandade Santa Casa de Misericordia de Porto Alegre New Anticancer Drugs Unit R Prof Annes Dias, 295 Porto Alegre RS CEP 90020-090 Brazil 55 51 3214 8143	4
BRRJ	496	Renato Goncalves Martins, MD	Instituto Nacional de Cancerologia Praca da Cruz vermelha, 23 80 andar sala 36 Rio De Janeiro CEP 20230-130 Brazil	17
CAAJ	105	Stewart Rorke, MD	Dr. H. Bliss Murphy Cancer Centre 300 Prince Philip Drive St. John's NF A1B 3V6 Canada 709 777 7802	4
CABN	117	Wojciech Morzycki, MD	QEII Health Sciences Centre Nova Scotia Cancer Center 5820 University Avenue Halifax NS B3H 1V7 Canada 902 473 6019	3
CAGL	180	Francis Laberge, MD	Hopital Laval Center de Pneumologie 2725 Chemin Ste-Foy Ste-Foy QC G1V 4G5 Canada 418 656 4747	8
CAHC	190	Vera Hirsh, MD	McGill University Clinical Trials Operations 546 Pine Avenue West Montreal QC H2W 1S6 Canada 514 842 1231	26
CAHF	192	Renaud Whittom, MD	Hopital Du Sacre-Coeur 5400 boul. Gouin Montreal QC H4J 2C5 Canada 514 338 2050	5
CAHN	199	Joseph Ayoub, MD	Hopital Notre-Dame du CHUM 1560, rue Sherbrooke Est, Pavillon Simard 2e etage, local z-2911 Montreal QC H2L 4M1 Canada 514 890 8200	11
CAKK	223	Richard Gregg, MD	Kingston Regional Cancer Centre 25 King Street West Kingston ON K7L 5P9 Canada 613 544 2630 ext 4505	1
CAKO	224	Scott Laurie, MD	Ottawa Regional Cancer Centre 503 Smyth Road Ottawa ON K1H 1C4 Canada 613 737 7700 ext 56809	6
CAKP	225	Rafal Wierzbicki, MD	Peterborough Regional Health Centre 384 Rogers Street Peterborough ON K9H 7B6 Canada	4
CALC	227	Brian Findlay, MD	Hotel Dieu Health Sciences Hospital, Niagara Oncology - Clinical Trials 155 Ontario Street St. Catharines ON L2R 5K3 Canada 905 682 6451 ext 905	14
CALM	229	Andrew Arnold, MD	Hamilton Regional Cancer Centre 699 Concession Street Hamilton ON L8V 5C2 Canada 905 387 9495	3
CALO	231	Rafal Wierzbicki, MD	Lakeridge Health Oshawa Durham Regional Cancer Centre 1 Hospital Court Oshawa ON L1G 2B9 Canada 905 576 8711	0
CALY	234	Labib Zibdawi, MB, ChB, ABIM, FRCP (C)	Southlake Regional Health Centre Community Cancer Clinic 596 Davis Drive Newmarket ON L3Y 2P9 Canada	3
CAME	239	Jacinta Meharchand, MD	Toronto East General Hospital 825 Coxwell Avenue Toronto ON M4C 3E7 Canada 416 469 3325	6
CAMG	240	Frances Shepherd, MD	Princess Margaret Hospital 610 Univeristy Avenue Suite 5-104 Toronto ON M5G 2M9 Canada 416 946 4522	22
CAMH	241	Jonathan Wilson, MD	Humber River Regional Hospital 200 Church Street Weston ON M9N 1N8 Canada 416 249 4367	3
CAMM	244	Ron Burkes, MD	Mount Sinai Hospital 1221-600 Univeristy Avenue Toronto ON M5G 1X5 Canada 416 586 5117	3
CAMN	245	Yee Ung, MD	Toronto-Sunnybrook Regional Cancer Centre 2075 Bayview Avenue Toronto ON M4N 3M5 Canada 416 480 4951	3
CAMR	247	Bryn Pressnail, MD	The Royal Victoria Hospital 201 Georgian Drive Barrie ON L4M 6M2 Canada 705 737 3432	2
CAMU	250	Robert Myers, MD	Credit Valley Hospital 2300 Eglinton Ave. W., Suite 509 Mississauga ON L5M 2V8 Canada 905 828 1910	3
CAPN	270	Jonathan Noble, MD	Northeastern Ontario Regional Cancer Centre 41 Ramsey Lake Road Sudbury ON P3E 5J1 Canada 705 522 6237	9

## CLINICAL REVIEW

Site Code	Site Number	Investigator	Institution/Address/Phone	No. Patients Randomized
CAPS	272	David Walde, MD	Group Health Centre 240 McNabb Street Saulte Ste. Marie ON P6B 1Y5 Canada 705 759 1234	5
CARM	281	Sri Navaratnam, MD	Cancer Care Manitoba 675 McDermot Avenue Winnipeg MB R3E 0V9 Canada 204 787 2882	2
CASA	282	Haji Chalchal, MD	Allan Blair Cancer Centre 4101 Dewdney Avenue Regina SK S4T 7T1 Canada 306 766 2691	4
CATC	296	Donald Morris, MD	Tom Baker Cancer Centre 1331 29th Street NW Calgary AB T2A 4Z2 Canada 403 944 1707	7
CATW	311	Michael Smylie, MD	Cross Cancer Institute Department of Medicine 11560 University Avenue Edmonton AB T6G 1Z2 Canada	19
CAVK	348	David Fenton, MD	BC Cancer Centre for the Southern Interior 399 Royal Avenue Kelowna BC V1Y 5L3 Canada 250 712 3900 ext 3930	8
CAVV	354	Heidi Martins, MD	BCCA-Vancouver Island Cancer Centre 2410 Lee Avenue Victoria BC V8R 6V5 Canada 250 519 5500	1
CLCL	481	Jorge Gutierrez, MD	Clinica Las Condes Lo Fontecilla 441 Las Condes Chile 56 2 2104060	3
DEDX	145	Ulrich Gatzemeier, MD	Zentrum für Pneumologie und Thoraxchirurgie Krankenhaus Grosshansdorf der LVA Wohrendamm 80 Grosshansdorf 22927 Germany 49 4102 601 181	10
DEDV	143	Hans Macha, MD	Lungenklinik Hermer Theo-Funcciusstr.1 Hermer D-58675 Germany 49 2372 9082201	0
DEEO	586	Joachim von Pawel, MD	Asklepios Fachkliniken München-Gauting Onkologische Abteilung Robert-Koch-Allee 2 Gauting D 82131 Germany	10
DEEU	587	Robert Loddenkemper, MD	Lungenklinik Heckeshorn Zum Heckeshorn 33, Berlin 14109 Germany 49 30 8002 2220	2
DEEY	567	Christian Manegold, MD	Thoraxklinik Heidelberg Amalienstrasse 5, Heidelberg 69126 Germany 49 6221 396638	0
GRGB	583	Alexandra Gerogianni, MD	District General Hospital of Chest Disease of Athens "SOTIRIA" 7th Pneumonology Clinic 152 Mesogion Avenue 115 27 Holgaros Athens Greece 30 21 07778611	10
HKHY	565	Raymond Tsz-Tong Chan, MD	Queen Mary Hospital Department of Clinical Oncology Pokfulam Hong Kong 852 2855 4661	8
HKHZ	554	Mei-Wan Yeung, MD	Pamela Youde Nethersole Eastern Hospital Department of Oncology 3 Lok Man Road Chai Wan Hong Kong	1
ILIB	206	Dov Flex, MD	Rabin Medical Center Beilinson Campus Oncology Institute Petach Tikva 49100 Israel 972 3 9377447/1	3
ILIK	523	Mirjana Cviljak Wollner, MD	RAMBAM Medical Center Oncology Institute 8 Alya Str. Bat-Galim Haifa Israel 972 4 854 3021	2
ILIL	524	David Loven, MD	Haemek Medical Center Oncology Institute Afula 18101 Israel 972 4 649 5540	4
ILIO	528	Haim Biran, MD	Kaplan Medical Center Oncology Institute Rehovot Israel	4
ILIP	529	Baruch Klein, MD	Rabin Medical Center Golda Campus Institute of Oncology Petach-Tiqva Israel 972 3 9372559	0
ILIQ	558	Ofer Merimsky, MD	Sourasky Medical Center Oncology Institute (Ichilov) Oncological Institute 6 Weisman Str, Tel Aviv 64239 Israel	0
ILIS	217	Mark Levitt, MD	Chaim Sheba Medical Center Oncological Institute Tel Hashomer 52621 Israel 972 3 5303088	1
ILIT	578	Arnold Cyjon, MD	Assaf Harofeh Medical Center Oncology Institute, P.O. Beer-Yaacov Zerifin 70300 Israel 972 8 9779713	9
MXMF	560	Jesus Lopez, MD	Centro Estatal de Cancerologia de Durango Av 5 de Febrero, Zona Centro, Durango 34000 Mexico 52 618 825 6482	6
MXMY	559	Jorge Robles, MD	Hospital Central Sur de Alta Especialidad, PEMEX Periferico Sur #4091 Col. Fuentes del Pedregal Mexico City CP 14140 Mexico 52 55 5645 1684 ext 51574	5

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Site Code	Site Number	Investigator	Institution/Address/Phone	No. Patients Randomized
MXMZ	480	German Calderillo, MD	Instituto Nacional de Cancerologia Av San Fernando #22 Col Seccion XVI Mexico City CP 14000 Mexico	4
NZAU	491	Timothy Christmas, MD	Green Lane Hospital Department of Respiratory Medicine Green Lane West Auckland 3 New Zealand 64 9 637000	2
NZSZ	479	Andrew Simpson, MD	Wellington Cancer Centre Wellington Hospital Private Bag 7902 Wellington South New Zealand 64 4 3855999 ext 5099	1
RORB	486	Mircea Dediu, MD	Oncology Institute Bucharest 252 Fundeni Street Sector 2 Bucharest Romania 40 2 12 406160	15
RORC	280	Tudor Ciuleanu, MD	Oncology Institute Ion Chiricuta 34-36 Gh. Bilascu Street Cluj-Napoca 3400 Romania 40 2 64 198361 ext 229	65
RORS	487	Monica Patran, MD	Clinical County Hospital of Sibiu 2-4 C. Coposu St. Sibiu 2400 Romania 40 2 69 215050	6
RORU	485	Lucian Miron, MD	St Spiridon University Hospital Oncology-Radiology Dept 1 Independentei Boulevard, Iasi 6600 Romania	6
SECB	564	Lars Ek, MD	University Hospital Dept of Pulmonary Medicine Lund SE-22185 Sweden 46 46 177 340	2
SESU	293	Bengt Bergman, MD	Sahlgrenska University Hospital Dept of Pulmonary Medicine Gothenburg SE-413 45 Sweden 46 31 342 1000	5
SGKR	500	Ross Andrew Lai Kit Soo, MD	National University Hospital Dept. of Haematology-Oncology 5 Lower Kent Ridge Road Singapore 119074 65 772 4624	13
SGPE	488	Eng Huat Tan, MD	National Cancer Centre Dept. of Medical Oncology 11 Hospital Drive Singapore 169610	28
THRE	513	Savitree Maoleekoonpaioj, MD	Pramongkutklao Hospital Division of Oncology Rama VI Road Phayathai Bangkok 10400 Thailand 66 2 644 4137	20
THRF	514	Sumitra Thongprasert, MD	Chiangmai University Department of Medicine Faculty of Medicine Chiangmai 50002 Thailand 66 53 945477	24
THRG	577	Arkorn Cheirsilpa, MD	National Cancer Institution of Thailand Division of Medical Oncology Rama VI Rd. Phayathai Bangkok 10400 Thailand	3
USAX	532	Charles Rudin, MD	University of Chicago Medical Center 5841 South Maryland Avenue, MC 2115 Chicago IL 60637 773 834 0783	3
USVY	592	Robert Livingston, MD	University of Washington Seattle Cancer Care Alliance MS G4-830 825 Eastlake Avenue E. Seattle Washington 98109 206 288 1085	0
ZAAS	482	Paul Ruff, MD	Rosebank Clinic Oncology Unit Rosebank Medical and Dental Studies 11 Sturdee Avenue Rosebank South Africa	6
ZAAZ	483	Louis Goedhals, MD	National Hospital Department of Oncotherapy University of Free State Roth Avenue Bloemfontein 9301 South Africa	0
ZAGE	507	Dayle Hacking, MD	Durban Oncology Centre 99 Jan Smuts Highway West Ridgerridge Durban 4091 South Africa 27 31 261 8221	3
ZAPK	503	R. W. Eek, MD	Mary Potter Oncology Centre Totius Street Groenkloof Pretoria South Africa 27 12 346 6894	0
ZAPP	504	Samuel Fourie, MD	Die Wilgers Hospital Wilgers Oncology Unit Denneboom Road Lynnwood Pretoria South Africa 27 12 807 2744	1
ZAPU	502	Conrad Jacobs, MD	St George's Hospital East Cape Oncology Centre 40 A Park Drive Port Elizabeth 6000 South Africa 27 41 373 6533	4
ZAZA	417	Paul Ruff, MD	Johannesburg Hospital University of Witwatersrand Faculty Health Science 7 York Road Parktown 2193 South Africa	4
ZAZP	432	Coenraad Slabber, MD	Univ. of Pretoria & Pretoria Academic Hospitals Dept Medical Oncology Dr. Savage Road Pretoria 1000 South Africa	1
ZAZS	435	Daniel Vorobiof, MD	Sandton Oncology Centre 159 Rivonia Road Morningside Sandton South Africa 27 11 883 0900	2

**5. Efficacy Results**

Patient enrollment in each of the 17 participating countries is summarized in Table 2.

**Table 2: Patient Enrollment**

Country	Erlotinib (N=488)		Placebo (N=243)		Total (N=731)	
	n	(%)	n	(%)	n	(%)
Canada	123	(25)	62	(26)	185	(25)
Brazil	104	(21)	53	(22)	157	(21)
Romania	63	(13)	29	(12)	92	(13)
Argentina	41	(8)	24	(10)	65	(9)
Thailand	31	(6)	16	(7)	47	(6)
Singapore	27	(6)	14	(6)	41	(6)
Australia	21	(4)	7	(3)	28	(4)
Germany	16	(3)	6	(2)	22	(3)
Israel	14	(3)	9	(4)	23	(3)
South Africa	14	(3)	7	(3)	21	(3)
Mexico	11	(2)	4	(2)	15	(2)
Greece	6	(1)	4	(2)	10	(1)
Hong Kong	6	(1)	3	(1)	9	(1)
Sweden	5	(1)	2	(<1)	7	(<1)
New Zealand	3	(<1)	0	(0)	3	(<1)
Chile	2	(<1)	1	(<1)	3	(<1)
United States	1	(<1)	2	(<1)	3	(<1)

The ITT population consisted of 731 patients. Four patients never received treatment: 3 patients in the erlotinib arm and 1 patient in the placebo arm. These 4 patients were included in the ITT analyses for efficacy but not in the safety analyses.

A summary of the baseline demographics and disease characteristics of patients enrolled in Study BR.21 is presented in Table 3, Demographic and disease characteristics were well balanced between the 2 treatment arms.

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**Table 3: Patient and Disease Characteristics**

Characteristics	Erlotinib (N=488)		Placebo (N=243)	
	N	(%)	n	(%)
<b>Gender</b>				
Female	173	(35)	83	(34)
Male	315	(65)	160	(66)
<b>Age (median)</b>		62 (34 - 86)		59 (32 - 88)
<b>Age (Years)</b>				
18-39	6	(1)	5	(2)
40-64	293	(60)	148	(61)
≥ 65	189	(39)	90	(37)
<b>Race</b>				
White	379	(78)	188	(77)
Black	18	(4)	12	(5)
Oriental	63	(13)	28	(12)
Other	28	(6)	15	(6)
<b>ECOG Performance Status</b>				
0	64	(13)	34	(14)
1	256	(52)	132	(54)
2	126	(26)	56	(23)
3	42	(9)	21	(9)
<b>Weight Loss in Previous 6 Months</b>				
< 5%	320	(66)	166	(68)
5 - 10%	96	(20)	36	(15)
> 10%	52	(11)	29	(12)
Unknown	20	(4)	12	(5)
<b>Smoking History</b>				
Never smoked	104	(21)	42	(17)
Current or Ex-smoker	358	(73)	187	(77)
Unknown	26	(5)	14	(6)
<b>Pack Years Smoked</b>				
Number of pack-years < 20	36	(7)	12	(5)
Number of pack-years 20	291	(60)	166	(68)
Number of pack-years unknown	57	(12)	23	(9)
<b>Histology</b>				
Adenocarcinoma	246	(50)	119	(49)
Squamous	144	(30)	78	(32)
Undifferentiated Large Cell	41	(8)	23	(9)
Mixed Non-Small Cell	11	(2)	2	(<1)
Other	46	(9)	21	(9)
<b>Stage of Disease at First Diagnosis</b>				
IA	8	(2)	3	(1)
IB	15	(3)	8	(3)
IIA	5	(1)	5	(2)
IIB	11	(2)	11	(5)
IIIA	41	(8)	22	(9)
IIIB	182	(37)	91	(37)
IV	226	(46)	103	(42)

	<b>Erlotinib (N=488)</b>		<b>Placebo (N=243)</b>	
	<b>N</b>	<b>(%)</b>	<b>n</b>	<b>(%)</b>
<b>EGFR Stain (% Cells)</b>				
0-9	74	(15)	37	(15)
10-24	17	(3)	14	(6)
25-49	12	(2)	9	(4)
50-74	22	(5)	13	(5)
75	27	(6)	13	(5)
Results Not Evaluable	24	(5)	10	(4)
Sample Not Available	312	(64)	147	(60)
<b>EGFR Status</b>				
Positive	78	(16)	49	(20)
Negative	74	(15)	37	(15)
Results Not Evaluable	24	(5)	10	(4)
Sample Not Available	312	(64)	147	(60)
<b>Time From Initial Diagnosis to the Most Recent Progression/Relapse (Months)</b>				
<6	78	(16)	47	(19)
6 - 12	161	(33)	79	(33)
>12	246	(50)	114	(47)
Missing	3	(<1)	3	(1)
Median		12.1		11.6
<b>Time From Initial Diagnosis to Randomization (Months)</b>				
<6	63	(13)	34	(14)
6 - 12	157	(32)	85	(35)
>12	268	(55)	124	(51)
Median		13.1		12.2
<b>Time From the Most Recent Progression/Relapse to Randomization (Months)</b>				
<6	472	(97)	230	(95)
6 - 12	11	(2)	9	(4)
>12	3	(<1)	1	(<1)
Missing	2	(<1)	3	(1)
Median		0.5		0.5

Regarding EGFR expression submission of pathology blocks or slides was voluntary and required a separate consent form. EGFR expression status was determined by [ ] using the DAKO EGFR pharmDx™ kit, without knowledge of treatment assignment. For BR.21, a positive EGFR expression was defined as having at least 10% of cells staining for EGFR.

Pathology blocks or slides (either from the time of initial diagnosis or at a subsequent relapse) were available and interpretable for 31% of the patients in the erlotinib arm and for 35% of the patients in the placebo arm. In the erlotinib arm, 16% of patients (representing 51% of the patients with known results) had a positive EGFR expression and 15% (49% of the patients with known results) had a negative expression, compared

with 20% and 15% (representing 57% and 43% of the patients with known results) in the placebo arm.

A summary of previous therapies is presented in **Table 4**.

**Table 4: Prior Therapy**

	<b>Erlotinib (N=488)</b>		<b>Placebo (N=243)</b>	
<b>Previous Therapy</b>				
Chemotherapy	488	(100)	243	(100)
Surgery	487	(100)	242	(100)
Radiation	264	(54)	143	(59)
Hormonal Therapy	1	(<1)	1	(<1)
Other Prior Therapy	2	(<1)	2	(<1)
<b>Number of Prior Chemotherapy Regimens</b>				
1	243	(50)	121	(50)
2	238	(49)	119	(49)
3	7	(1)	3	(1)
<b>Prior Platinum Therapy</b>				
No	34	(7)	19	(8)
Yes	454	(93)	224	(92)
<b>Prior Taxane Therapy</b>				
No	311	(64)	153	(63)
Yes	177	(36)	90	(37)
<b>Best Response to Prior Therapy</b>				
CR or PR	186	(38)	92	(38)
SD	166	(34)	83	(34)
PD	136	(28)	68	(28)

**Table 5** summarizes the signs and symptoms occurring in at least 10% of patients in the erlotinib arm by MedDRA preferred term and maximum NCI CTC grade. As expected, most patients had at least one sign or symptom at the start of the study. The incidence, distribution and severity of signs and symptoms were well balanced between the 2 treatment arms.

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**Table 5: Baseline signs and symptoms in ≥ 10% of patients**

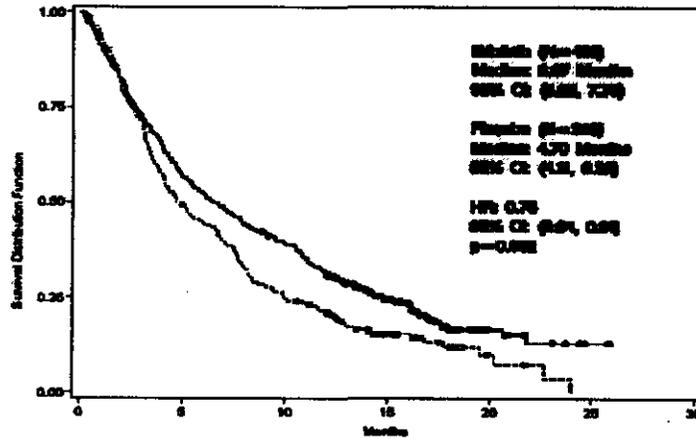
MedDRA Preferred Term	Erlotinib (N=488)						Placebo (N=243)					
	Any		1-2		3-4		Any		1-2		3-4	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total patients with any signs and symptoms	470	(96)	382	(78)	88	(18)	237	(98)	197	(81)	40	(16)
Dyspnea	320	(66)	276	(57)	44	(9)	159	(65)	144	(59)	15	(6)
Cough	301	(62)	301	(62)	0	(0)	141	(58)	140	(58)	1	(<1)
Fatigue	276	(57)	255	(52)	21	(4)	134	(55)	122	(50)	12	(5)
Anorexia	173	(35)	168	(34)	5	(1)	77	(32)	75	(31)	2	(<1)
Chest pain	115	(24)	102	(21)	13	(3)	58	(24)	51	(21)	7	(3)
Neuropathy	80	(16)	76	(16)	4	(<1)	33	(14)	30	(12)	3	(1)
Bone pain	70	(14)	56	(11)	14	(3)	36	(15)	32	(13)	4	(2)
Nausea	62	(13)	62	(13)	0	(0)	35	(14)	35	(14)	0	(0)
Constipation	57	(12)	55	(11)	2	(<1)	35	(14)	33	(14)	2	(<1)
Hemoptysis	49	(10)	49	(10)	0	(0)	21	(9)	21	(9)	0	(0)

**Survival Analyses**

Analyses of survival and PFS were performed using the ITT population. 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 or lost to follow-up (7 patients were lost to follow-up; 4 erlotinib treated patients and 3 placebo treated patients). The 106 erlotinib treated patients and the 31 patients in the placebo arm who were alive had been followed for 12.0 to 25.9+ months, while the 7 patients who were lost to follow-up had been followed for 0.4 to 11.1 months. A total of 28 of 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,

The primary stratified Log-Rank test of survival, as specified in the SAP, required the following baseline factors at randomization be used to adjust the analysis: ECOG PS (0 or 1 vs 2 or 3), best response to prior therapy (CR or PR vs SD vs PD), number of prior regimens (1 vs 2), exposure to prior platinum (prior platinum vs no prior platinum), and also the EGFR status (positive: ≥ 10% expression vs negative: < 10% expression vs unknown). The adjusted HR for death in the erlotinib arm relative to the placebo arm was 0.73 (95% CI, 0.60 – 0.87) (p = 0.001). The median overall survival, estimated from univariate Kaplan-Meier curves, was 6.67 months in the erlotinib arm (95% CI, 5.52 – 7.79 months) compared with 4.70 months in the placebo arm (95% CI, 4.11 – 6.28 months) (Figure 2). The difference between these survival curves was statistically significant (Log Rank p-value = 0.002). The actuarial 12-month survival rates were 31.2% and 21.5%, respectively, for the erlotinib and placebo arms. The unstratified hazard ratio (HR) for death in the erlotinib arm relative to the placebo arm, estimated from a univariate Cox model, was 0.76 (95% CI, 0.64 – 0.91), a 24% reduction in risk of death and a 32% improvement in risk of survival.

Figure 2: Overall survival



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Table 6 and Figure3 presents a summary of survival by pretreatment characteristics of patient subsets (per sponsor).

Table 6: Univariate survival analysis by subset

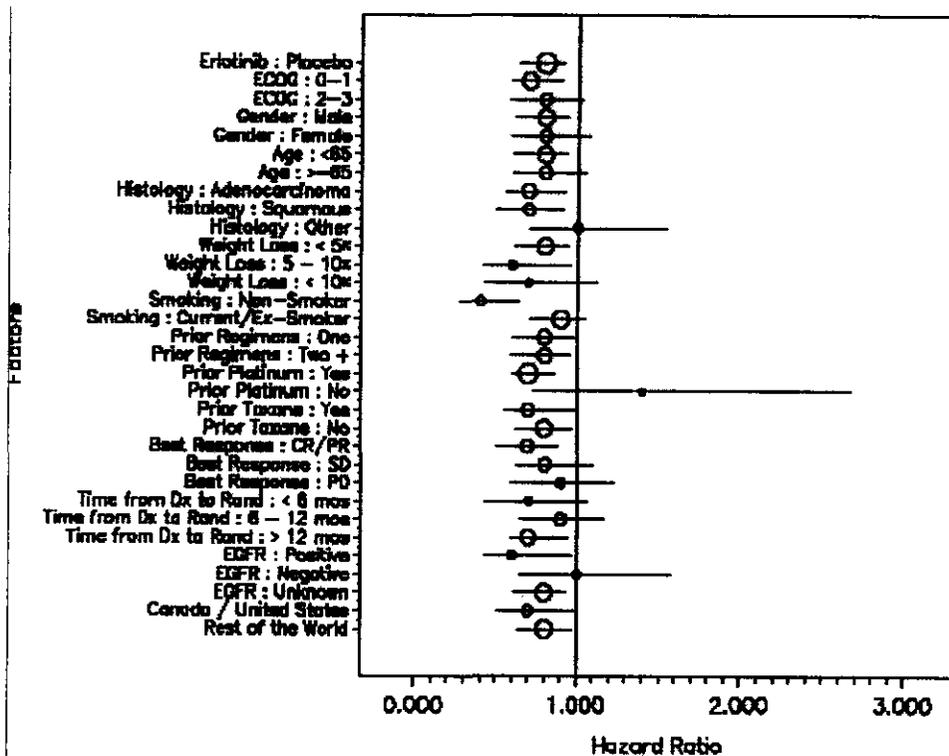
Pretreatment Characteristics	N	Erlotinib Median Survival (Months) (95% CI)	Placebo Median Survival (Months) (95% CI)	Hazard Ratio (95% CI)	Log-Rank p-value
<b>Exposure to Prior Taxane</b>					
Yes	177	7.20 (5.09, 9.43)	90 4.67 (3.55, 7.06)	0.74 (0.56, 0.99)	0.038
No	311	6.11 (5.22, 7.79)	153 4.96 (4.01, 6.70)	0.78 (0.63, 0.97)	0.022
<b>EGFR Status</b>					
Positive	78	10.71 (7.92, 12.85)	49 3.84 (3.12, 6.80)	0.65 (0.43, 0.97)	0.033
Negative	74	5.16 (3.91, 8.28)	37 7.49 (3.09, 12.02)	1.01 (0.65, 1.57)	0.958
Unknown	336	6.05 (4.93, 7.20)	157 5.09 (4.14, 6.60)	0.76 (0.61, 0.93)	0.008
<b>Smoking Status</b>					
Never Smoked	104	12.25 (10.61, 16.13)	42 5.62 (3.55, 8.05)	0.42 (0.28, 0.64)	<0.001
Current or Ex-Smoker	358	5.52 (4.67, 6.51)	187 4.63 (3.88, 6.18)	0.87 (0.71, 1.05)	0.141
Unknown	26	4.63 (2.66, 10.71)	14 5.96 (3.25, 10.78)	1.09 (0.54, 2.21)	0.803
<b>Gender</b>					
Male	315	5.72 (4.83, 7.00)	160 4.45 (3.65, 5.88)	0.76 (0.62, 0.94)	0.009
Female	173	8.44 (6.47, 10.71)	83 6.18 (4.11, 8.31)	0.80 (0.59, 1.07)	0.128

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<b>Age</b>						
< 65	299	6.11 (4.96, 7.89)	153	5.09 (4.11, 6.80)	0.75 (0.61, 0.93)	0.009
>65	189	7.00 (5.42, 8.97)	90	4.35 (3.52, 6.70)	0.79 (0.60, 1.04)	0.095
<b>Histology</b>						
Adenocarcinoma	246	7.75 (5.42, 10.48)	119	5.36 (4.11, 7.79)	0.71 (0.56, 0.92)	0.008
Squamous	144	5.57 (4.67, 7.00)	78	3.58 (3.15, 4.34)	0.67 (0.50, 0.90)	0.007
Other	98	6.97 (5.16, 8.64)	46	7.29 (5.09, 8.71)	1.04 (0.70, 1.54)	0.840
<b>Weight Loss in Previous 6 Months</b>						
< 5%	320	8.28 (7.23, 10.48)	166	6.18 (4.53, 7.52)	0.77 (0.62, 0.95)	0.014
5 - 10%	96	4.01 (3.19, 6.11)	36	3.61 (3.02, 5.55)	0.63 (0.42, 0.95)	0.026
> 10%	52	2.64 (2.17, 3.75)	29	2.07 (1.84, 3.84)	0.70 (0.43, 1.12)	0.129
Unknown	20	8.28 (3.91, 16.36)	12	10.73 (6.74, 12.85)	0.74 (0.32, 1.71)	0.482
<b>Time From Initial Diagnosis to Randomization (Months)</b>						
< 6	63	3.45 (1.87, 7.82)	34	3.10 (2.40, 4.11)	0.68 (0.43, 1.06)	0.088
6 - 12	157	5.22 (4.34, 6.74)	85	4.67 (3.58, 6.60)	0.87 (0.65, 1.16)	0.340
> 12	268	8.33 (7.00, 10.48)	124	6.65 (4.27, 7.62)	0.75 (0.59, 0.95)	0.016
<b>Region</b>						
Canada/United States	124	6.37 (4.73, 9.49)	64	4.30 (3.09, 6.93)	0.71 (0.51, 0.98)	0.035
Rest of the World	364	6.70 (5.36, 7.89)	179	5.03 (4.11, 6.60)	0.79 (0.64, 0.96)	0.018

In the Forest Plot (Figure 3) the size of each bubble represents the size of that respective subpopulation, and the bars represent the confidence interval for that data set.

Figure 3: Survival analysis by subset



A question was raised as to whether the improved overall survival results of erlotinib treatment was accounted for by EGFR positive patients. This issue was discussed with the sponsor.

The sponsor stated that “A series of subsets ... were examined in exploratory univariate analyses to assess the robustness of the overall survival results (Table 6). These are underpowered exploratory analyses, and no adjustments were made for the multiplicity of inferences from these subsets.”

The small numbers of patients with evaluable EGFR expression status produce estimates of hazard ratios (HR) with wide confidence intervals (CI). For example, although the HR among EGFR-negative patients is 1.01, the lower bound of the 95% CI is 0.65, which is the point estimate of the HR among EGFR-positive patients. The 95% CIs for these two subsets are overlapping, indicating that the HR for EGFR-negative patients is not significantly different than the HR for EGFR-positive patients.

In addition FDA analysis indicates that the patient populations who received erlotinib who were EGFR positive or EGFR negative were prognostically different. (Table 7).

**Table 7: Prognostic factors in erlotinib treated patients by EGFR expression**

	EGFR Positive N=78		EGFR Negative N=74	
Age at diagnosis				
≤65	44	56.4%	57	77.0%
>65	34	43.6%	17	23.0%
Stage at Diagnosis				
IA or IB	4	5.1%	4	5.4%
IIA or IIB	2	2.6%	4	5.4%
IIIA	14	18.0%	8	10.8%
IIIB	30	38.5%	18	24.3%
IV	28	36.0%	40	54.1%
Histology				
Adenocarcinoma	39	50.0%	45	60.8%
Squamous	26	33.3%	15	20.3%
Large Cell Undifferentiated	8	10.3%	5	6.8%
Other	5	6.4%	9	12.2%
Sex				
Male	56	71.8%	40	54.0%
Female	22	28.2%	34	46.0%
Response to Prior Therapy				
CR/PR	41	52.6%	24	32.4%
SD	30	38.5%	37	50.0%
PD	7	9.0%	13	17.6%
Weight loss in the preceding 6 months				
<5%	51	65.4%	41	55.4%
5-10%	17	21.8%	18	24.3%
>10%	5	6.4%	11	14.9%
Unknown	5	6.4%	4	5.4%
Time Initial Diagnosis to Randomization (mo)				
≤ 6	2	2.6%	7	9.5%
7-12	23	29.5%	20	27.0%
13-24	37	47.4%	25	33.8%
25-36	7	9.0%	15	20.3%
>36	9	11.5%	7	9.5%
ECOG Performance Status				
0-1	53	68.0%	52	70.3%
2	20	25.6%	18	24.3%
3	5	6.4%	4	5.4%
Prior Regimens				
1	24	30.8%	30	40.5%
2	54	69.2%	44	59.5%

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	EGFR Positive N=78		EGFR Negative N=74	
Prior Platinum				
Yes	71	91.0%	74	100.0%
No	7	9.0%	0	0.0%
Prior Taxane				
Yes	26	33.3%	26	35.1%
No	52	66.7%	48	64.9%

Favorable prognostic features of EGFR positive patients included older age (43.6% vs. 23.6% > age 65), fewer patients who were stage IV at diagnosis (36.0% vs. 54.1%), more objective responses to prior therapy (52.6% vs. 32.4%), less weight loss in the 6 months preceding study entry (65.4% with <5% weight loss vs. 53.4%) and longer time from initial diagnosis to randomization.

**Table 8** presents survival results of erlotinib treated patients. As indicated there is a non-statistically significant trend toward increased survival outcome for the EGFR positive patients. This does not answer the question as to whether beneficial survival results in EGFR positive patients result from erlotinib being a targeted therapy or whether EGFR positive status is a favorable prognostic factor.

**Table 8: Survival of Tarceva Treated Patients**

EGFR Known Population	Positive N=78	Negative N=74	Hazard Ratio <sup>1</sup> (95% CI)	P-value <sup>2</sup>
# 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)		

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

**Table 9** presents survival results of placebo treated patients. This table suggests that survival is shorter for EGFR positive patients. As such it does not support the hypothesis that EGFR positivity is a favorable prognostic factor. Small numbers in both data-sets prevent definitive conclusions, however.

**Table 9: Survival of Placebo Treated Patients**

EGFR Known Population	Positive N=49	Negative N=37	Hazard Ratio <sup>1</sup> (95% CI)	P-value <sup>2</sup>
# 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)		

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

Because of a suggestion that severity of skin rash might correlate with survival an unplanned exploratory analysis of this relationship was performed. In the 363 erlotinib-treated patients who developed rash, the median survival was 9.49 months (95% CI: 7.95 – 10.91), and it was 2.22 months (95% CI: 1.71 – 2.76) for the 122 erlotinib-treated patients with no rash. A similar pattern was also observed for the patients in the placebo arm. There were several notable differences in pretreatment prognostic characteristics favoring patients who did experience rash. These differences, together with the confounding effects due to the time dependent nature of both rash and survival, preclude a definitive interpretation of these observations.

**Response rate**

An in-depth medical and focused independent radiology review was performed for the first 330 randomized patients to critically assess objective response. For the remaining 401 patients, the Investigators' assessment and NCIC CTG Physician Coordinator was used. The objective response rates in the erlotinib arm were 12/195 (6.2%) and 26/232 (11.2%) for the first 330 and last 401 randomized patients (Table 10).

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**Table 10: Best Response - Measurable Disease Patients**

Response	First 330 patients				Remaining 401 patients				All patients			
	Erlotinib (N=195)		Placebo (N=94)		Erlotinib (N=232)		Placebo (N=117)		Erlotinib (N=427)		Placebo (N=211)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Complete (CR)	1	(<1)	0	(0)	3	(1.3)	1	(<1)	4	(<1)	1	(<1)
Partial (PR)	11	(5.6)	0	(0)	23	(9.9)	1	(<1)	34	(8.0)	1	(<1)
Stable (SD)	73	(37.4)	16	(17.0)	77	(33.2)	40	(34.2)	150	(35.1)	56	(26.5)
Progression (PD)	77	(39.5)	61	(64.9)	87	(37.5)	60	(51.3)	164	(38.4)	121	(57.3)
Inevaluable or Not Applicable(IN/NA)	33	(16.9)	17	(18.1)	42	(18.1)	15	(12.8)	75	(17.6)	32	(15.2)

Stratification	Erlotinib			Placebo		
	n/N	(%)	95% C I	n/N	(%)	95%CI
Overall Response Rate (CR + PR) - First 330 Pts	12/195	(6.2)	(3.2, 10.5)	0/94	(0)	N/A
Overall Response Rate (CR+ PR) - Last 401 Pts	26/232	(11.2)	(7.5, 16.0)	2/117	(1.7)	(0.2, 6.0)
Overall Response Rate (CR + PR) - All Pts	38/427	(8.9)	(6.4, 12.0)	2/211	(<1)	(0.1, 3.4)

For patients with nonmeasurable disease only one additional patient (MXMY0763) with a pleural effusion achieved a CR while treated with erlotinib.

*Comment: FDA analysis confirmed the above response rate.*

Response rates were higher among women (14.4%) than men (6.0%), higher among patients with adenocarcinomas (13.9%) than patients with squamous carcinomas (3.8%) or other histologies (4.5%), higher among patients who never smoked (24.7%) than current or ex-smokers (3.9%), higher among patients with EGFR-positive tumors (11.6%) than patients with EGFR-negative tumors (3.2%).

As previously discussed, however, these differences in response rates did not necessarily translate into differential clinical benefit from erlotinib relative to placebo with respect to overall survival. For example, although women had a higher response rate, the survival benefit was numerically superior for males (HR = 0.76 for males and 0.80 for females).

Response duration is summarized in Table 11. The duration of objective responses in the erlotinib arm ranged from 9.7 to 57.6+ weeks.

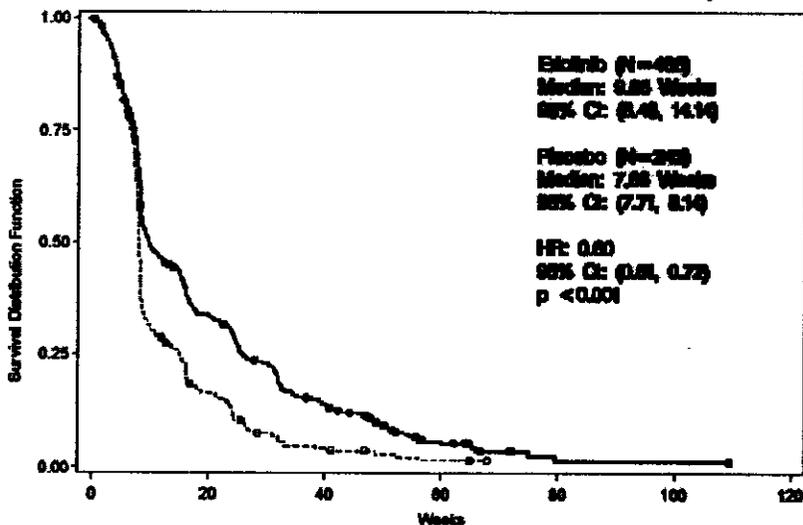
**Table 11: Response duration**

Population	Erlotinib (N=427)			Placebo (N=211)		
	n	Median (Weeks)	95%CI*	n	Median (Weeks)	95%CI
Complete response (CR)	4	NA	(17.29, .)	1	12.6	NA
Overall response (PR+CR)	38	34.3	(24.71, 44.14)	2	15.9	(12.57, 19.29)
Stable Disease (SD)	150	24.4	(23.57, 25.57)	56	18.7	(16.14, 24.00)

**Progression free survival**

The FDA reviewer revised some of the progression dates submitted by the sponsor. The PFS curves shown in Figure 4 represent sponsor and reviewer consensus on progression and censor dates for all study patients

**Figure 4: Progression free survival**



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The median PFS, estimated from univariate Kaplan-Meier curves, was 9.86 weeks in the erlotinib arm (95% CI, 8.43 – 14.14 weeks) compared with 7.86 weeks in the placebo arm (95% CI, 7.71 to 8.14 weeks). The HR for progression in the erlotinib arm relative to the placebo arm, estimated from a univariate Cox model, was 0.60 (95% CI, 0.51 – 0.72). The difference between these PFS curves was statistically significant (Log Rank p-value < 0.001).

The prognostic effects of the stratification factors on PFS was also evaluated. In univariate analyses, the factors that were associated with worse PFS were: ECOG PS 2 or 3, and PD as best response to prior therapy. Neither the number of prior regimens nor exposure to prior platinum was predictive of PFS. EGFR status was marginally

associated with PFS (Table 12). In the multivariate analysis, after adjustment for the treatment effect, ECOG PS and PD as best response to prior therapy remained statistically significant ( $p = 0.001$  and  $0.040$ , respectively). Consistent with the results for overall survival, the small numbers of patients with evaluable EGFR expression status produce estimates of hazard ratios with quite wide CIs. The 95% CIs for patients with EGFR-positive or EGFR-negative tumors are overlapping, indicating that the HR for EGFR-negative patients is not significantly different than the HR for EGFR-positive patients. Neither the number of prior regimens nor prior exposure to platinum was statistically significant in the multivariate model.

**Table 12: PFS by EGFR Status**

	Erlotinib		Placebo		Hazard Ratio (95% CI)	Log-Rank p-value
	N	Median PFS Weeks (95% CI)	N	Median PFS Weeks (95% CI)		
EGFR Status						
Positive	78	16.14 (12.00, 24.00)	49	7.86 (7.29, 8.43)	0.49 (0.33, 0.72)	<0.001
Negative	74	8.14 (7.86, 9.43)	37	8.14 (7.86, 12.00)	0.91 (0.59, 1.39)	0.657
Unknown	336	9.71 (8.29, 15.00)	157	7.86 (7.57, 8.14)	0.56 (0.46, 0.70)	<0.001

**Quality of Life per sponsor**

Quality of life was assessed by patients using the EORTC QLQ-C30 questionnaire and the lung cancer module, QLQ-LC13. Questionnaires 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 within 4 weeks of the end of treatment. The primary endpoints in the quality of life analysis were time to deterioration of cough, dyspnea, and pain. Deterioration was prespecified in the SAP as a change from baseline of 10 points or more on a 100-point scale at any time-point after the baseline assessment. Table 13 indicates those patients who completed a baseline plus at least 1 follow-up questionnaire

**Table 13: Patients Evaluable for Quality of Life Assessment**

	<b>Erlotinib (N=488)</b>		<b>Placebo (N=243)</b>	
	<b>n</b>	<b>(%)</b>	<b>n</b>	<b>(%)</b>
<b>Cough Scores</b>				
Baseline + at least 1 Follow-up	305	(63)	156	(64)
<b>Dyspnea Scores</b>				
Baseline + at least 1 Follow-up	360	(74)	182	(75)
<b>Pain Scores</b>				
Baseline + at least 1 Follow-up	363	(74)	182	(75)

In the majority of cases, non-completion of questionnaires was related to a lack of translations. There was no Thai translation of the full questionnaire available, and no Romanian translation of the QLQ-LC13. In addition to the lack of translation, the most frequent reasons why questionnaires were not collected was because patients went off study prior to the 4-week assessment time-point and because of illness that prohibited completion of the questionnaire.

Baseline scores for each of the three symptoms were well balanced between treatment arms (Table 14). Maximal cough was reported by 5% of the patients in the erlotinib and placebo arm at baseline, as was dyspnea. Maximal pain was reported by 3% and 5% of the patients in the erlotinib and placebo arms, respectively.

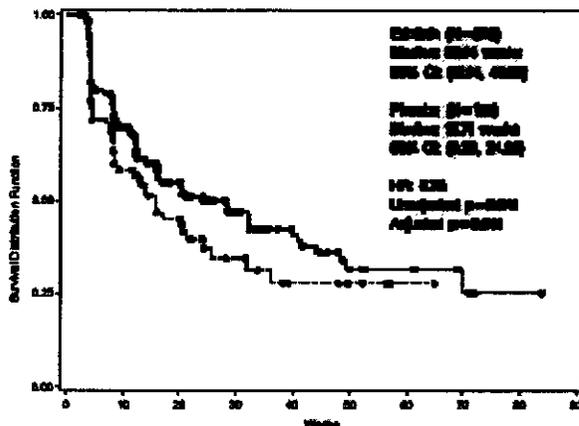
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**Table 14: Baseline symptom scores**

	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)

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 5. 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).

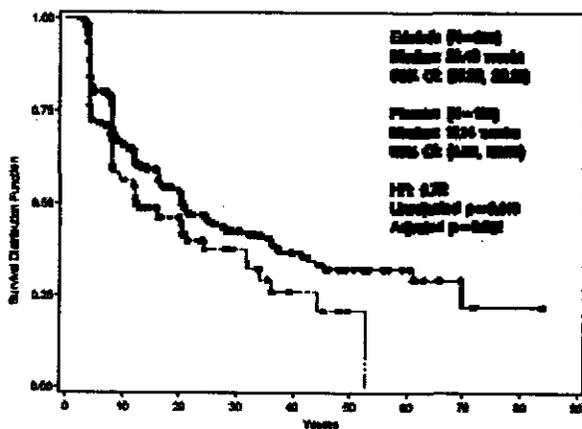
**Figure 5: Time to Deterioration of Cough**



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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 6. The medians 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).

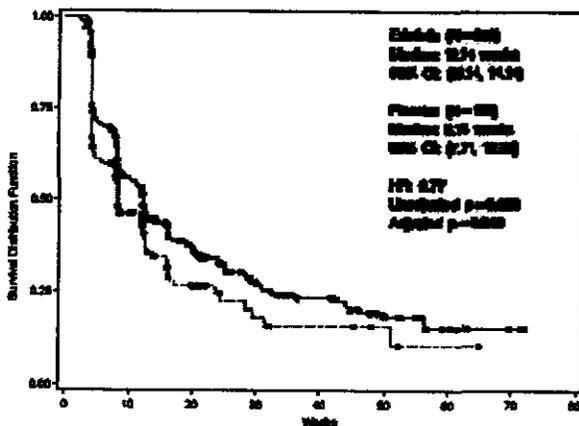
Figure 6: Time to Deterioration of Dyspnea



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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 7. 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).

Figure 7: Time to deterioration of pain



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To confirm that the difference in time to symptom deterioration between the 2 treatment arms could not be ascribed to an imbalance in the use of palliative measures (concomitant medication, radiotherapy), the administration of palliative treatment was compared between the two treatment arms.

**Table 15** presents the increase in medication use from baseline to on-study for the three main symptoms: cough, dyspnea and pain. At baseline, 8.2% of patients treated with erlotinib and 8.3% of patients treated with placebo were receiving cough medications. During the study an additional 15.7% of patients treated with erlotinib and 13.5% of placebo-treated patients required cough medications.

At baseline, 43.9% of patients treated with erlotinib and 46.2% of patients treated with placebo were receiving dyspnea medications. During the study an additional 33.3% of patients treated with erlotinib and 25.8% of patients treated with placebo required dyspnea medications.

At baseline, 37.7% of patients treated with erlotinib and 42.3% of patients treated with placebo who were included in the analysis of time to deterioration of pain were receiving non-opiate analgesics, and an additional 20.9% of patients treated with erlotinib and 19.8% of patients treated with placebo were receiving opiates (total 58.7% and 62.1%). During the study an additional 31.1% of patients treated with erlotinib and 33.5% of patients treated with placebo required an increase in pain medications (no pain medications at baseline to analgesics or opiates, or nonopiate analgesics to opiates) during the study.

These comparisons did not take into account time on study. Since the median duration of treatment was 9.6 weeks for patients in the erlotinib arm and 8.0 weeks in the placebo arm, the differences would become even smaller if adjusted for time on study.

Symptom benefits, therefore, are not a result of increased use of concomitant palliative medications.

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**Table 15: Palliative Therapy**

	Erlotinib			Placebo			Fisher's Exact p-value
	N	Number of Patients Taking Medications	(%)	N	Number of Patients Taking Medications	(%)	
<b>Baseline usage of Palliative Therapy for Cough, Dyspnea, and Pain</b>							
Cough	305	25	(8.2)	156	13	(8.3)	1.000
Dyspnea	360	158	(43.9)	182	84	(46.2)	0.648
Pain: analgesics + opiates	363	137 + 76	(58.7)	182	77 + 36	(62.1)	0.460
<b>Increased Usage of Palliative Therapy During Study</b>							
Cough	305	48	(15.7)	156	21	(13.5)	0.582
Dyspnea	360	120	(33.3)	182	47	(25.8)	0.077
Pain	363	113	(31.1)	182	61	(33.5)	0.626

**Comments on the symptom deterioration analysis**

There are problems with the symptom deterioration analyses. Regarding dyspnea the sponsor's win is on the single dyspnea symptom item from the QLQ-C30. There is no significant difference in the three item dyspnea symptom domain from the LC-13 instrument (See Table 16, from the statistical analysis performed by Dr. Sridhara). Similarly for pain the pain items from the QLQ-30 instrument show statistical significance in favor of Tarceva while chest pain is only of borderline significance, other pain sites are not significant and pain medication is not significant.

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**Table 16: Time to deterioration of symptoms**

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
Global QOL Scale	1.205 (0.862, 1.686)	0.2619
Hemoptysis Single Item	0.982 (0.656, 1.471)	0.9306
Dyspnea Symptom Domain	0.893 (0.699, 1.142)	0.3452
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

**Post-study therapy**

**Table 17** summarizes post-study anticancer therapy. A total of 99 patients (21%) in the erlotinib arm and 74 patients (30%) in the placebo arm received either chemotherapy or EGFR inhibitors after discontinuing the study. If survival times for patients who received post-study therapy were censored at the start of this therapy, the survival curve for erlotinib remained significantly better than for placebo

**Table 17: Post-study therapy**

	<b>Erlotinib (N=488)</b>		<b>Placebo (N=243)</b>	
	<b>n</b>	<b>(%)</b>	<b>n</b>	<b>(%)</b>
Number of patients with any post-study therapy <sup>a</sup>	163	(33)	101	(42)
Chemotherapy	91	(19)	56	(23)
EGFR inhibitors	8	(2)	18	(7)
Radiotherapy	93	(19)	52	(21)

a. Patients could have received more than 1 type of therapy.

**Supporting Study**

**Study A248-1007: A Phase II Multicenter Open-Label Trial of OSI-774 Following Failure of Platinum Based Combination Chemotherapy in Patients with Advanced Non-Small Cell Lung Cancer**

This was a single arm, open-label, multicenter Phase II trial 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. Serial measurements of all disease sites were performed every 8 weeks and response and PFS were assessed using WHO criteria (conventional) and RECIST. Efficacy was further evaluated by periodic assessments of health-related quality of life (HQoL).

The 57 study patients had failed a median of 2 prior chemotherapy regimens (range 1 to 8). Sixty percent of the patients were female and 91% were white. The median age was 62 years (range: 31 – 83). Most patients (77%) had an ECOG PS of 1, and the majority were ex-smokers (74%). The most common tumor type was adenocarcinoma (61%). The median time from initial diagnosis to study entry was 18 months (range: 4 – 137).

Of the 57 patients in the ITT population, 2 achieved a CR and 5 had a PR for an objective response rate of 12.3% (95% CI, 5.1-23.7%). Twenty-two patients had SD (38.6%) and 28 patients (49.1%) had progressive disease (PD). The median duration of response was 19.7 weeks (range: 11.7 – 80.3). Response rates were identical regardless of type of prior chemotherapy or whether the patient had received 1, 2, or more prior regimens. With 9 patients still alive and censored in the analysis, the median overall survival was 8.4 months (95% CI, 4.8-13.9 months). The 1-year survival rate was 40.4% (95% CI, 27.6-54.2%). With 5 patients censored in the analysis, the median PFS was 9.0 weeks (95% CI, 8.0-15.3 weeks).

**Other Phase III Trials**

**OSI2298g: A Phase III, Randomized, Double-Blind, Multicenter Trial Of Tarceva. (Erlotinib) plus Chemotherapy (Carboplatin and Paclitaxel) versus**

**Chemotherapy Alone in Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer Who Have Not Received Prior Chemotherapy (“TRIBUTE”)**

The primary objective of this trial was to evaluate the efficacy of erlotinib when combined with carboplatin/paclitaxel versus carboplatin/paclitaxel alone for treatment of NSCLC as measured by duration of survival. A secondary objective was time to symptomatic progression [Lung Cancer Symptom Scale (LCSS)]. The ITT population comprised 1079 patients (539 patients in the erlotinib arm and 540 patients in the placebo arm). This trial demonstrated that the addition of erlotinib to chemotherapy resulted in no increase in duration of survival compared with patients treated with chemotherapy alone. The median survival was 324 days (10.8 months, 95% CI, 288 – 381 days) in the erlotinib arm versus 319 days (10.6 months, 95% CI, 285 – 344 days) in the placebo arm, Log Rank  $p = 0.9517$ . There was also no increase in objective response rate or time to disease progression. There was a statistically significant benefit in terms of time to symptom progression, but this did not correlate with a clinical benefit as measured by overall survival and response. Subset analysis did not demonstrate a correlation between level of EGFR expression and survival.

**Study BO16411: A Randomized, Double-Blind, Placebo Controlled, Multicenter, Phase III Study of Tarceva. plus Chemotherapy (Cisplatin and Gemcitabine) versus Chemotherapy Alone in Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) Who Have Not Received Prior Chemotherapy. (“TALENT”)**

The primary objective of this trial was to evaluate the efficacy of erlotinib when combined with cisplatin plus gemcitabine versus cisplatin plus gemcitabine alone for treatment of NSCLC as measured by duration of survival. The ITT population comprised 1172 patients (586 patients in the erlotinib arm and 586 patients in the placebo arm). There was no difference in overall survival between the 2 treatment groups: 301 days (95% CI, 274 – 315 days) in the erlotinib group versus 309 days (95% CI, 282 – 343 days) in the placebo group (hazard ratio of 1.06). There was no benefit of erlotinib treatment over placebo treatment on progression free survival (167 days erlotinib versus 179 days placebo). The proportion of patients with objective responses was similar for each of the treatment groups (31.5% in the erlotinib group and 29.9% in the placebo group). Data from the 376 analyzable tumor samples showed no correlation between HER1/EGFR expression (graded as 0, 1+, 2+ or 3+) and erlotinib treatment effect as measured by either survival or response. The median time to symptomatic progression (defined as a worsening from baseline in the average symptom burden index by at least 25%) was 68 days in erlotinib-treated patients compared with 76 days in the placebo group.

**D. Efficacy Conclusions**

Study BR.21 was a pivotal Phase III study conducted in patients with Stage IIIB/IV NSCLC after failure of at least 1 standard chemotherapy regimen. Patients enrolled in this study were treated once daily with doses of 150 mg of erlotinib or equivalent placebo. Erlotinib provided a statistically significant prolongation of survival (median

survival = 6.67 months erlotinib vs 4.70 months placebo, HR = 0.73, p < 0.001) and progression-free survival (PFS). An erlotinib treatment effect was demonstrated in all secondary endpoints, including response rate and time to deterioration of lung cancer symptoms (cough, dyspnea and pain).

Study A248-1007 provided supportive evidence of erlotinib activity in NSCLC.

## VII. Integrated Review of Safety

### A. Brief Statement of Conclusions

In study BR.21 most erlotinib treated patients experienced rash and diarrhea, generally grades 1 and 2. This only occasionally resulted in dose-reduction or discontinuation of treatment. Gastrointestinal symptoms included anorexia, nausea and vomiting, again generally grades 1 and 2. Treatment effects on hematology and chemistry parameters were mild. A total of 6 patients developed serious interstitial lung disease (ILD)-like events, 4 patients in the erlotinib arm (0.8%) and 2 patients in the placebo arm (0.8%). No new or unexpected safety findings have emerged.

### B. Description of Patient Exposure

Table 18 and Table 19 summarize the dose intensity and relative dose intensity, respectively, by treatment arm. The protocol specified dose intensity was 150 mg/day for both arms. As indicated in Table 18 most patients had a relative dose intensity of  $\geq$  90%.

**Table 18: Dose Intensity**

		<b>Erlotinib (N=485)</b>	<b>Placebo (N=242)</b>
Dose intensity (mg/day)	Median	150	150
	Mean	138	146
	Range	44 - 152	83 - 153
Relative Dose intensity (%)	Median	100	100
	Mean	92	98
	Range	29 - 101	55 - 102

**Table 19: Relative Dose Intensity**

	<b>Erlotinib (N=485)</b>		<b>Placebo (N=242)</b>	
	<b>n</b>	<b>(%)</b>	<b>n</b>	<b>(%)</b>
>90%	376	(78)	226	(93)
80-90%	23	(5)	7	(3)
<80%	86	(18)	9	(4)

**Table 20** summarizes the exposure by weeks of treatment within each treatment arm.

**Table 20: Summary of Exposure by Weeks of Treatment**

Cumulative Weeks	Erlotinib (N=485)		Placebo (N=242)	
	n	(%)	n	(%)
≤ 4	84	(17)	41	(17)
>4 - 8	110	(23)	86	(36)
>8 - 16	118	(24)	60	(25)
>16 - 26	60	(12)	30	(12)
>26 - 52	82	(17)	22	(9)
> 52	31	(6)	3	(1)
Median	9.6		8.0	
Range	0.1 - 110.6		1.1 - 64.7	

**Table 21** and **Table 22** summarize the dose reductions and interruptions.

As expected, the most frequent causes for dose reduction in the erlotinib arm were rash (10%) and diarrhea (4%).

**Table 21: Patients with Dose Reductions**

	Erlotinib (N=485)		Placebo (N=242)	
	n	(%)	n	(%)
No Dose Reductions	391	(81)	238	(98)
Dose Reduction to 100 mg	75	(15)	3	(1)
Dose Reduction to 100 mg then to 50 mg	19	(4)	1	(<1)
<b>Reason For Dose Reduction</b>				
Rash	48	(10)	0	(0)
Other Reason	31	(6)	4	(2)
Diarrhea	20	(4)	0	(0)
Intercurrent Illness	4	(<1)	0	(0)
Patient Missed Dose	3	(<1)	0	(0)
Patient Request	1	(<1)	0	(0)

**Table 22: Patients with Dose Interruptions**

	<b>Erlotinib (N=485)</b>		<b>Placebo (N=242)</b>	
	<b>n</b>	<b>(%)</b>	<b>n</b>	<b>(%)</b>
No Dose Interruption	185	(38)	122	(50)
<b>Dose Interrupted for &gt; 7 consecutive days</b>	<b>105</b>	<b>(22)</b>	<b>26</b>	<b>(11)</b>
Other reason	38	(8)	5	(2)
Rash	35	(7)	0	(0)
Intercurrent illness	18	(4)	11	(5)
Diarrhea	9	(2)	0	(0)
Patient request	6	(1)	3	(1)
Patient missed dose	4	(<1)	1	(<1)
Patient non-compliance	4	(<1)	4	(2)
Administrative	2	(<1)	3	(1)
Not applicable	1	(<1)	0	(0)
<b>Dose Interrupted for &gt; 14 consecutive days</b>	<b>38</b>	<b>(8)</b>	<b>10</b>	<b>(4)</b>
Rash	15	(3)	0	(0)
Other reason	12	(2)	3	(1)
Diarrhea	3	(<1)	0	(0)
Intercurrent illness	3	(<1)	5	(2)
Patient request	2	(<1)	1	(<1)
Patient missed dose	1	(<1)	0	(0)
Patient non-compliance	1	(<1)	1	(<1)
Administrative	0	(0)	1	(<1)

**C. Methods and Specific Findings of Safety Review**

Safety assessments consisted of monitoring and recording all adverse events (AEs) and SAEs (with their severity and relationship to study drug), the regular monitoring of hematology, and blood chemistry, regular measurement of vital signs, the performance of physical examinations and documentation of all concomitant medications and therapies.

Table 23 summarizes the overall safety in this study by treatment arm.

**Table 23: Overall Summary of Safety**

	<b>Erlotinib (N=485)</b>		<b>Placebo (N=242)</b>	
	<b>n</b>	<b>(%)</b>	<b>n</b>	<b>(%)</b>
Patients with at least one AE	481	(99)	233	(96)
AE's Regardless of Causality by worst severity				
Grade 1	22	(5)	27	(11)
Grade 2	157	(32)	65	(27)
Grade 3	195	(40)	87	(36)
Grade 4	107	(22)	54	(22)
Patients with at least one SAE	165	(34)	68	(28)
Patients who died on treatment or within 30 days	155	(32)	71	(29)

Table 24 summarizes adverse events occurring in  $\geq 10\%$  of patients regardless of causality.

Table 24: Adverse Events in  $\geq 10\%$  of Patients Regardless of Causality

MedDRA System Organ Class (SOC) Preferred Term	Erlotinib (N=485)						Placebo (N=242)					
	Any		1-2		3-4		Any		1-2		3-4	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total patients with any AE	481	(99)	179	(37)	302	(62)	233	(96)	92	(38)	141	(58)
<b>Skin disorders</b>	379	(78)	334	(69)	45	(9)	58	(24)	57	(24)	1	(<1)
Rash	363	(75)	321	(66)	42	(9)	40	(17)	40	(17)	0	(0)
Pruritus	61	(13)	59	(12)	2	(<1)	12	(5)	12	(5)	0	(0)
Dry skin	60	(12)	60	(12)	0	(0)	9	(4)	9	(4)	0	(0)
<b>Gastrointestinal disorders</b>	358	(74)	281	(58)	77	(16)	121	(50)	107	(44)	14	(6)
Diarrhea	261	(54)	232	(48)	29	(6)	44	(18)	42	(17)	2	(<1)
Nausea	158	(33)	143	(29)	14	(3)	59	(24)	55	(23)	4	(2)
Vomiting	113	(23)	102	(21)	11	(2)	47	(19)	43	(18)	4	(2)
Stomatitis	83	(17)	79	(16)	4	(<1)	8	(3)	8	(3)	0	(0)
Constipation	68	(14)	61	(13)	7	(1)	35	(14)	33	(14)	2	(<1)
Abdominal pain	52	(11)	41	(8)	11	(2)	17	(7)	13	(5)	4	(2)
<b>General disorders</b>	322	(66)	215	(44)	106	(22)	154	(64)	90	(37)	64	(26)
Fatigue	250	(52)	163	(34)	86	(18)	108	(45)	59	(24)	49	(20)
Chest pain	83	(17)	62	(13)	21	(4)	53	(22)	38	(16)	15	(6)
<b>Respiratory, thoracic and mediastinal disorders</b>	319	(66)	171	(35)	148	(31)	149	(62)	80	(33)	69	(29)
Dyspnea	198	(41)	64	(13)	134	(28)	84	(35)	21	(9)	63	(26)
Cough	159	(33)	141	(29)	18	(4)	70	(29)	64	(26)	6	(2)
Hemoptysis	72	(15)	65	(13)	7	(1)	33	(14)	29	(12)	4	(2)
<b>Metabolism and nutrition disorders</b>	265	(55)	203	(42)	61	(13)	100	(41)	80	(33)	20	(8)
Anorexia	250	(52)	207	(43)	43	(9)	93	(38)	81	(33)	12	(5)
<b>Nervous system disorders</b>	175	(36)	133	(27)	42	(9)	78	(32)	54	(22)	24	(10)
Headache	85	(18)	79	(16)	6	(1)	38	(16)	32	(13)	6	(2)
Neuropathy	49	(10)	34	(7)	15	(3)	23	(10)	18	(7)	5	(2)
<b>Musculoskeletal and connective tissue disorders</b>	166	(34)	134	(28)	32	(7)	91	(38)	63	(26)	28	(12)
Bone pain	51	(11)	35	(7)	16	(3)	29	(12)	14	(6)	15	(6)
<b>Infections and infestations</b>	157	(32)	114	(24)	43	(9)	49	(20)	36	(15)	13	(5)
Infection	116	(24)	96	(20)	20	(4)	37	(15)	32	(13)	5	(2)
<b>Eye disorders</b>	131	(27)	126	(26)	5	(1)	21	(9)	20	(8)	1	(<1)
Conjunctivitis	57	(12)	54	(11)	3	(<1)	5	(2)	4	(2)	1	(<1)
Keratoconjunctivitis sicca	56	(12)	56	(12)	0	(0)	8	(3)	8	(3)	0	(0)

The incidence of AEs was more frequent ( $> 5\%$  difference) in the erlotinib arm than in the placebo arm in the following categories: skin and subcutaneous tissue disorders (78% vs 24%), gastrointestinal disorders (74% vs 50%), metabolism and nutrition disorders (55% vs 41%), infections and infestations (32% vs 20%), and eye disorders (27% vs 9%), as detailed below.

**Skin and subcutaneous tissue disorders**

The most commonly occurring skin AE, regardless of causality, was rash. Grade 3 and 4 rash occurred in 8% and < 1%, respectively, of erlotinib-treated patients while no placebo-treated patients experienced severity greater than CTC Grade 2. Rash was the cause of discontinuation of protocol therapy in 7 erlotinib-treated patients (1%) and resulted in dose reduction in 10% and interruption for > 7 days in 7% of the patients. No patients in the placebo arm required similar interventions due to rash.

Median time to onset of first rash was 8 days for erlotinib-treated patients with rash compared with 18 days to first rash for placebo-treated patients with rash.

**Gastrointestinal disorders**

Diarrhea was the second most common AE regardless of causality in the erlotinib arm and occurred in 54% of the patients compared with 18% in the placebo arm. Diarrhea was mostly mild or moderate (Grade 1 – 2: 48%) with 6% of patients experiencing a worst severity of Grade 3 and < 1% of Grade 4. In the placebo arm, 5% were Grade 2, < 1% Grade 3 and no Grade 4 events were reported. Seven erlotinib-treated patients (1%) discontinued due to diarrhea and 9 (2%) had dose interruptions for >7 days.

Median time to onset of first diarrhea was 12 days for erlotinib-treated patients with diarrhea compared with 19 days to first diarrhea for placebo-treated patients.

Nausea and vomiting were also common events experienced by 33% vs 24% and 23% vs 19%, respectively, of the patients in the erlotinib and placebo arms. Stomatitis was much more frequent in the erlotinib arm (17%) compared with the placebo arm (3%). Less than 1% of the erlotinib-treated patients experienced Grade 3 stomatitis and < 1% of placebo treated patients experienced Grade 2 stomatitis as the worst severity.

**Infections**

More erlotinib-treated patients developed infections compared with placebo (32% vs 20%). Most (24% vs 15%) were reported as “Infection without neutropenia”. The majority of these “infections” were nonserious Grade 1 or 2 severity (20% vs 13%) and none were Grade 4 or associated with neutropenia.

**Eye disorders**

The most frequent eye disorders were conjunctivitis and keratoconjunctivitis sicca (dry eyes) experienced by 12% each of the erlotinib-treated patients compared with 2% and 3%, respectively, in the placebo-treated patients. The worst severity was Grade 3 occurring in < 1% in each arm. Keratitis was reported in 3% of erlotinib-treated patients compared with 1% of placebo, however, all except one case was less than Grade 2 and none were reported as medically significant or resulting in discontinuation of protocol therapy.

**Metabolism and nutrition disorders**

Anorexia was the primary reported disorder (52%, erlotinib arm vs 38%). The majority of the events in this system organ class (SOC) were Grade 1 – 2 in severity (CTC) but 11% of the patients in the erlotinib arm experienced Grade 3 events compared with 7% in the placebo arm while 2% and 1% in each arm, respectively, were Grade 4 severity.

**Other adverse events**

Other common AEs occurring in  $\geq 25\%$  of erlotinib-treated patients are typically associated with the underlying disease. These include fatigue (52% vs 45%), dyspnea (41% vs 35%), and cough (33% vs 29%).

**Serious Adverse Events**

Table 25 presents the incidence of patients with SAEs regardless of causality occurring in at least 2% of patients.

**Table 25: SAEs Occurring in  $> 2\%$  of Patients Regardless of Causality**

MedDRA System Organ Class Preferred Term	Erlotinib (N=485)						Placebo (N=242)					
	Any		1-2		3-4		Any		1-2		3-4	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total patients with any SAE	165	(34)	19	(4)	146	(30)	68	(28)	4	(2)	64	(26)
<b>Respiratory, thoracic and mediastinal disorders</b>	79	(16)	5	(1)	74	(15)	35	(14)	3	(1)	32	(13)
Dyspnea	62	(13)	1	(<1)	61	(13)	29	(12)	1	(<1)	28	(12)
Hemoptysis	11	(2)	5	(1)	6	(1)	5	(2)	1	(<1)	4	(2)
<b>Gastrointestinal disorders</b>	50	(10)	14	(3)	36	(7)	7	(3)	2	(<1)	5	(2)
Diarrhea	14	(3)	6	(1)	8	(2)	0	(0)	0	(0)	0	(0)
Vomiting	13	(3)	5	(1)	8	(2)	2	(<1)	0	(0)	2	(<1)
Nausea	11	(2)	3	(<1)	8	(2)	0	(0)	0	(0)	0	(0)
<b>General disorders and administration site conditions</b>	38	(8)	10	(2)	28	(6)	12	(5)	2	(<1)	10	(4)
Fatigue	23	(5)	4	(<1)	19	(4)	6	(2)	0	(0)	6	(2)
<b>Infections</b>	37	(8)	8	(2)	29	(6)	7	(3)	1	(<1)	6	(2)
Pneumonia	19	(4)	3	(<1)	16	(3)	3	(1)	1	(<1)	2	(<1)
Infection	11	(2)	4	(<1)	7	(1)	1	(<1)	0	(0)	1	(<1)
<b>Metabolic disorders</b>	29	(6)	6	(1)	23	(5)	14	(6)	5	(2)	9	(4)
Dehydration	18	(4)	4	(<1)	14	(3)	6	(2)	1	(<1)	5	(2)
Anorexia	15	(3)	5	(1)	10	(2)	4	(2)	2	(<1)	2	(<1)

**Interstitial Lung Disease**

The following MedDRA preferred terms were used for this analysis: pneumonitis, pulmonary infiltrate, pulmonary fibrosis, radiation fibrosis-lung, and lung disorder.

At baseline, 3% of the patients in the erlotinib arm and 5% of patients in the placebo arm had ILD-like conditions. Pulmonary fibrosis accounted for the majority of the events.

On-study, ILD-like AEs, regardless of causality, were reported for 3% in the erlotinib arm and 1% in the placebo arm. During this period, lung infiltration accounted for the majority mainly because pulmonary fibrosis was not treatment-emergent.

ILD-like SAEs regardless of causality are summarized in Table 26.

**Table 26: ILD-like SAEs**

MedDRA Preferred Term	n	Erlotinib (N=485)			n	Placebo (N=242)		
		Any (%)	1-2 (%)	3-4 (%)		Any (%)	1-2 (%)	3-4 (%)
Total patients with any AE	4	(<1)	(<1)	(<1)	2	(<1)	(0)	(<1)
Lung infiltration	2	(<1)	(0)	(<1)	1	(<1)	(0)	(<1)
Pneumonitis	2	(<1)	(<1)	(<1)	1	(<1)	(0)	(<1)

A total of 6 patients developed serious ILD-like events, 4 patients in the erlotinib arm (0.8%) and 2 patients in the placebo arm (0.8%). The 3 cases of pneumonitis (erlotinib: CASA0189 and CAHC0738; placebo: BRPL0594) were all considered treatment-related and 2 of them (erlotinib: CAHC0738; placebo: BRPL0594) resulted in death due to protocol toxicity. Histological information was available for 2 patients. An autopsy was performed on CAHC0738 (erlotinib arm) who died 8 days after the last dose of study drug. She only received a total of 8 doses of erlotinib. The histopathological evaluation of lung tissue revealed focal alveolar damage suggesting early interstitial pneumonia possibly due to a drug reaction. Patient BRPL0594 (placebo arm) developed respiratory insufficiency after 55 days on study. A transbronchial biopsy was inconclusive showing only congestive lung without neoplasia. The patient died due to suspected drug-induced pneumonitis. The third patient with pneumonitis (CASA0189) was diagnosed after 275 days on study. Radiological tests showed evidence of progressive bronchogenic carcinoma with superimposed pneumonia. The patient discontinued treatment and improved.

All 3 cases of lung infiltration (erlotinib: BRRJ0266 and AUGA0190; placebo: BRBM0388) were considered unrelated to protocol therapy. The event was fatal in 1 erlotinib treated patient (BRRJ0266) while the other patients had concurrent fatal pneumonia (erlotinib: AUGA0190) or fatal respiratory insufficiency due to NSCLC (placebo: BRBM0388). The diagnostic information and clinical presentation of all possible ILD cases are variable and mostly confounded by a number of other factors. All patients were smokers and had received prior chemotherapy. Patient AUGA0190 (erlotinib arm) had received prior chest radiation and had baseline radiation pneumonitis. Patient BRPL0594 (placebo arm) was receiving concomitant amiodarone, which is associated with lung toxicity. The histological diagnoses of the lung cancer varied with 2 patients having adenocarcinoma (CASA0189, BRBM0388), 3 patients with squamous cell carcinoma (AUGA0190, BRRJ0266, and BRPL0594), and 1 patient diagnosed with undifferentiated large cell carcinoma (CAHC0738).

Overall, the incidence of serious ILD-like conditions in the study is 0.8% in each treatment arm and the incidence of histologically confirmed cases is 0.2% (erlotinib arm only, 1 patient).

### **Bleeding disorders**

Overall, 24% of patients in the erlotinib arm and 17% of patients in the placebo arm experienced any bleeding disorder. Hemoptysis was most frequent but balanced between the 2 treatment arms (15% vs 14%), followed by epistaxis, which was more frequent in erlotinib-treated patients (7% vs < 1%). Most events were of Grade 1 severity. Serious episodes of hemoptysis were reported for 11 erlotinib-treated patients (2%) and 5 placebo-treated patients (2%). The lung cancer histology was squamous cell carcinoma in 7 of 11 erlotinib-treated patients and 4 of 5 placebo-treated patients suggesting this histological type is more prone to bleeding. To correct for the longer survival time observed in the erlotinib arm, the incidence of serious bleeding per patient weeks was calculated. The rate in the erlotinib arm was 7.64 per patient weeks compared with 18.22 in the placebo arm.

### **Laboratory Evaluation**

#### **Hematology**

Table 27 describes the baseline and worst CTC grade on-study for hemoglobin, WBC, granulocytes and platelets by treatment arm.

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ON ORIGINAL**

**Table 27: Hematology Toxicity (Shift table)**

	Baseline Grade	Erlotinib (N=485)						Placebo (N=242)						
		Maximum NCI CTC Grade						Maximum NCI CTC Grade						
		Unk	0	1	2	3	4	Unk	0	1	2	3	4	
Total Hgb (g/dL)	Unk	0	0	1	0	0	0	0	0	0	0	0	0	0
	0	10	77	60	6	0	0	2	45	20	3	0	0	
	1	40	17	154	39	4	3	21	13	81	25	2	0	
	2	12	0	23	26	4	0	10	0	7	9	3	0	
	3	3	0	1	0	2	1	1	0	0	0	0	0	
WBC (10 <sup>9</sup> /L)	Unk	0	0	0	0	0	0	0	0	0	0	0	0	
	0	65	384	15	7	0	0	34	199	4	1	0	0	
	1	1	6	4	0	0	0	0	3	0	0	0	0	
	2	0	2	0	0	0	0	0	0	1	0	0	0	
	3	0	1	0	0	0	0	0	0	0	0	0	0	
Granulocytes (10 <sup>9</sup> /L)	Unk	2	4	0	0	0	0	3	0	0	0	0	0	
	0	107	355	6	3	1	0	53	180	2	2	0	0	
	1	2	2	0	0	0	0	0	0	0	0	0	0	
	2	0	1	0	0	0	0	1	0	1	0	0	0	
	3	0	1	0	0	0	0	0	0	0	0	0	0	
Platelets (10 <sup>9</sup> /L)	Unk	0	0	0	0	0	0	0	0	0	0	0	0	
	0	64	377	22	2	0	1	34	191	12	0	0	0	
	1	2	6	7	0	1	0	0	2	3	0	0	0	
	2	0	0	1	0	1	0	0	0	0	0	0	0	
	3	1	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0		

As indicated in the Table hematologic toxicity was mild with infrequent grade 3/4 toxicity on either arm.

**INR**

Baseline and on-study INR values were available for 33 erlotinib-treated patients and 14 placebo treated patients who were receiving warfarin.. Shifts to values that may be associated with significant bleeding risks (INR ≥ 4) were seen in 11 erlotinib-treated patients (26%) and 4 placebo-treated patients (21%). None of these patients, however, experienced serious clinical bleeding.

**Clinical biochemistry**

Shifts from baseline of 2 or more grades for ALT occurred in 12 erlotinib-treated patients and none of the placebo-treated patients. The observed shifts were from baseline Grade 0 or 1 to a maximum Grade 2 suggesting mainly mild effects on liver function in approximately 3% of the erlotinib-treated patients. The incidence of shifts from a baseline Grade 0 to Grade 1 was similar in each treatment arm.

A similar pattern was seen for bilirubin. In the erlotinib arm, 19 patients (4%) developed

a significant shift compared with 3 patients (1%) in the placebo arm. The maximum severity was Grade 2, except for 1 erlotinib-treated patient (CATC0147) who developed a worst grade of 3. New liver metastases were found during the same time period in this patient. Similarly, pre-existing or new liver metastases could account for the bilirubin elevation in 5 other erlotinib-treated patients.

Significant shifts from baseline in serum creatinine were seen in 6 erlotinib-treated patients whose worst severity grade were 2, changed from baseline Grade 0. The changes were transient and reversible to Grade 0 in 3 patients (ARAN0403, BRBL0247, ILIB0735), returned to Grade 1 in 1 patient (CAPS0100), and unknown in the 2 remaining patients (BRPL0427, CATC0147) since they died from pulmonary embolism and PD, respectively. Confounding and contributing factors included renal colic with hematuria (BRPL0427), possible urinary tract infection, dehydration, and renal insufficiency (CATC0147), and diarrhea, dehydration or vomiting (BRPL0427, CAPS0100).

**ECG**

The proportion of patients having shifts from normal ECG at baseline to abnormal on-study was the same in each treatment arm (3% each). The most frequent events were atrial fibrillation (5 patients vs 2 patients) and sinus tachycardia (3 patients vs 2 patients). No QT-prolongations were reported.

**Deaths**

Of all 727 patients who received at least one study drug dose, 155 (32%) and 71 (29%) of the erlotinib and placebo treated patients, respectively, died during treatment or within 30 days of the last dose. Table 28 summarizes the cause of death. As indicated, the rate of death from complications of protocol therapy, per investigator attribution, is 0.8% in the erlotinib arm and 0.4% in the placebo arm.

**Table 28: Patients Who Died On-Study or Within 30 Days of Last Treatment**

	Erlotinib (N=485)		Placebo (N=242)	
	n	(%)	n	(%)
Number of patients who died within 30 days of last treatment	155	(32)	71	(29)
Cause of Death				
NSCLC	131	(27)	62	(26)
Other condition or circumstance	18	(4)	7	(3)
Combination NSCLC and non-protocol treatment complication	2	(<1)	0	(0)
Combination NSCLC and protocol treatment complication	2	(<1)	0	(0)
Toxicity from protocol treatment	2	(<1)	1	(<1)
Non-protocol treatment complication	0	(0)	1	(<1)

**D. Adequacy of Safety Testing**

Safety testing was adequate. There is considerable experience with EGFR TK inhibitors in this and other studies. There were no new safety concerns.

**D. Summary of Critical Safety Findings and Limitations of Data**

Erlotinib therapy was well tolerated by most patients. As expected, most patients experienced rash and/or diarrhea, generally grades 1 and 2. This only occasionally resulted in dose-reduction or discontinuation of treatment. Gastrointestinal symptoms included anorexia, nausea and vomiting, again generally mild. No new or unexpected safety findings emerged from this placebo-controlled study. The incidence of interstitial pneumonitis was 0.8% in each treatment arm. Patients receiving concurrent warfarin treatment had INR values outside the normal range (26% in the erlotinib arm vs 21% in the placebo arm). Treatment effects on hematology and chemistry parameters were small.

In conclusion, this large, randomized, placebo-controlled trial has confirmed the favorable safety profile of erlotinib in a population of patients with advanced NSCLC. The most common events were rash and diarrhea, mostly mild or moderate in severity, as expected for this class of agents. No other safety concerns have emerged.

**VIII. Dosing, Regimen, and Administration Issues**

None

**IX. Use in Special Populations**

**A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation**

There was no significant effect of gender on either efficacy or safety results. Erlotinib exposure was similar among males and females.

**B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

There was no significant effect of race/ethnicity on either efficacy or safety results. 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  $\geq 65$  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.

**C. Evaluation of Pediatric Program**

Erlotinib has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

**D. Comments on Data Available or Needed in Other Populations**

**1. Renal or Hepatic Impairment**

Erlotinib should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. Erlotinib has not been studied in patients with significant renal or hepatic impairment.

**2. Pregnancy**

**Pregnancy - Category**

Erlotinib has been shown to cause maternal toxicity with associated embryo/fetal lethality and abortion in rabbits when given at doses that result in plasma drug concentrations of approximately 4 times those in humans (AUCs at 150 mg daily dose). At plasma drug concentrations of 1-2 times those in humans, there was no increased incidence of embryo/fetal lethality or abortion in rabbits or rats.

No teratogenic effects were observed in rabbits or rats.

There are no adequate and well-controlled studies in pregnant women using Erlotinib. Women of childbearing potential must be advised to avoid pregnancy while on Erlotinib. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus. If Erlotinib is used during pregnancy, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

**Nursing Mothers**

It is not known whether Erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of Erlotinib on infants have not been studied, women should be advised against breast-feeding while receiving Erlotinib therapy.

**X. Conclusions and Recommendations**

**A. Conclusions**

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. 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.

Of concern is whether these results apply only to EGFR positive patients. Study patients with EGFR-positive tumors seem to derive more survival benefit than patients with EGFR-negative tumors (10.7 months versus 5.2 months). The problem is that pathology blocks or slides to determine EGFR expression status (DAKO EGFR pharmDx™ kit) were available and the results were interpretable only for 31% of the patients in the erlotinib arm and for 35% of the patients in the placebo arm.

The small numbers of patients with evaluable EGFR expression status produce estimates of hazard ratios (HR) with wide confidence intervals (CI). For example, although the HR among EGFR-negative patients is 1.01, the lower bound of the 95% CI is 0.65, which is the point estimate of the HR among EGFR-positive patients. The 95% CIs for these two subsets are overlapping.

It is of importance to obtain additional data to resolve this question. The sponsor has been asked to obtain additional tissue blocks for analysis but material from only a small number of additional patients will be available. Therefore, the sponsor has also been asked to collect EGFR status data for patients who have received, or will receive gefitinib in ongoing studies.

**B. Recommendations**

Regular Approval

**Binding phase 4 commitments**

The sponsor will be required to obtain pathology blocks to determine EGFR status in future studies.

**XI. Appendix 1: Inspections**

The following sites were selected for inspection by the review division.

Country	Investigator	Screened	Enrolled	Evaluable
Canada	Frances A. Shepherd, MD	22	22	22
	Vera S. Hirsh, MD	26	26	26

**Frances A. Shepherd, M.D.**

Inspection Dates: July 23- August 21, 2003

There was one previous inspection of Dr. Shepherd on November 11, 1999. A FDA-483 was issued to address some drug accountability issues and the report was classified VAI.

**Methodology:** Inspection assignments were issued to the field office.

**What was inspected:** Twenty-two subjects were enrolled. Records for all 22 subjects were reviewed during the inspection. All case report forms were examined and compared to source documents such as patients' charts.

**Limitations of inspection:** None.

**General observations/commentary:**

No FDA-483 was issued.

**Recommendation:** Data from this site are acceptable

**Vera S. Hirsh, M.D.**

**Inspection Dates:** August 9 - August 12, 2004.

**Methodology:** Inspection assignments were issued to the field office.

**What was inspected:** Twenty-six subjects were enrolled. Records for 26 subjects were reviewed during the inspection. The case report forms were examined and compared to source documents such as patients' charts to verify disease states. The source data for tumor measurements and staging were reviewed. The adverse event reporting/documentation and quality of life case report forms were examined.

**Limitations of inspection:** None.

**General observations/commentary:**

No FDA-483 was issued. No significant deviations were noted. The study appeared to be well controlled, monitored, and documented.

**Recommendation:** Data from this site are acceptable.

### **Overall Assessment Of Findings And General Recommendations**

Drs. Hirsh and Shepherd adhered to good clinical practices governing the conduct of clinical investigations. There was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, and were available for the duration of the study, and that all enrolled subjects received the assigned study drug and had clinical and laboratory parameters recorded, completed the study, and had their primary efficacy endpoints captured as specified in the protocols and amendments and correctly reported to the sponsor.

### **Appendix 2: Protocol BR.21 and Amendments**

National Cancer Institute Of Canada Clinical Trials Group (NCIC CTG)

**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**

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**Dr. Andrea Bezjak Study Coordinators: Dianne Johnston Aleksandra Trajkovic Sponsor (Canada):**

**NCIC CTG Sponsor (Other Countries): OSI Pharmaceuticals / Designee**

**APPEARS THIS WAY  
ON ORIGINAL**

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**1.0 OBJECTIVES**

### 1.1 Primary Objective

To compare overall survival ( OS) between the 2 arms

### 1.2 Secondary Objectives

To compare progression- free survival ( PFS)

To compare response rates ( RR) To estimate response duration

To compare the nature, severity, and frequency of toxicities between the 2 arms

To compare the Quality of Life as measured by EORTC QLQC30 and QLQ LC13

To correlate the expression of tissue EGFR levels (at diagnosis) with outcomes and response to treatment (Appendix VI)

To measure and correlate trough levels of OSI-774 with clinical responses and/ or adverse events (Appendix VIII).

## 2.0 BACKGROUND INFORMATION AND RATIONALE

### 2.1 Non- Small Cell Lung Cancer

Lung cancer is the leading cause of cancer- related death in North America and Europe, and approximately 85% of patients in whom this neoplasm is diagnosed will die of this disease. Seventy- five percent of lung cancer is non- small cell lung cancer (NSCLC).

Approximately 75% of patients with NSCLC present with unresectable or metastatic disease and are essentially incurable. The median survival of patients with metastatic NSCLC is historically about 4 months when treated with best supportive care (Bunn 1998[a]). The primary goal of therapy is to palliate symptoms and prolong disease-free and overall survival. Systemic chemotherapy has demonstrated palliative benefit and modest prolongation of survival, and combination chemotherapy with cytotoxic agents is now the standard of care for good performance patients with metastatic disease (see Section 2.2). ( Bunn 1998[a], Carney 1998, Bunn 1998[b], Sweeney 1998). Despite these advances, patients with unresectable or metastatic disease will eventually relapse and succumb to their disease. A recent trial comparing docetaxel to best supportive care was the first to document that patients with non- small cell lung cancer ( NSCLC) could benefit from second- line chemotherapy after cisplatin- based first- line regimens ( Shepherd, 2000). Benefit could be measured in terms of prolongation of time to progression and overall survival, improvement in symptoms, reduction in the need for cancer- related medicines, in particular narcotic pain medications, and improvement in several quality of life indices. Patients of all ages and performance status 0, 1 or 2 demonstrated improvement in survival with docetaxel, as did those who had been refractory to prior platinum treatment. However, patients with weight loss  $\geq$  10%, high lactate dehydrogenase level, multiorgan involvement or liver involvement did not benefit from treatment. Furthermore, when docetaxel was given as third- line treatment or more, there was no prolongation of survival. Although single- agent docetaxel is now considered standard second- line therapy for NSCLC there remain patients who do not appear to benefit from docetaxel, such as those

patients with poor performance status, or who are unsuitable or unwilling to receive further cytotoxic therapy. For patients who have failed docetaxel, few therapeutic options are available, and include supportive care and palliative radiation. Clearly, new strategies for the management of patients with NSCLC are required.

## 2.2 Chemotherapy for NSCLC

Older, platinum- based combination therapies prolong survival modestly compared to best supportive care when given as first line therapy ( Bunn 1998[ a], Sweeney 1998). Recently, several new chemotherapeutic agents ( paclitaxel, gemcitabine, docetaxel, vinorelbine and irinotecan) have shown good single- agent activity. In randomized phase III trials, these agents in combinations with platinum have been associated with improved quality of life (QOL) and improved survival of 8 to 10 months (Carney 1998, Bunn 1998 [b]).

## 2.3 EGFR and Inhibitors of EGFR

The control of cell growth is mediated by a complex network of signalling pathways responsive to external influences, such as growth factors, as well as to internal controls and checks. Epidermal growth factor (EGF) was one of the first growth factors to be described. It was shown to be mitogenic, an effect mediated by the binding of EGF to a cell surface receptor ( EGFR). Subsequent investigations revealed EGFR to be one of a group of closely related receptors now referred to as the EGFR family, which includes EGFR, HER2, HER3 and HER4. These family members are considered to be important in the development, progression and aggressive behaviour of human cancers.

EGFR is a transmembrane glycoprotein with a single polypeptide chain of 1186 amino acids ( 170 kilodaltons) and consists of extracellular, transmembrane and intracellular regions. Known ligands for EGFR include EGF, TGF-  $\alpha$ , epiregulin, heregulin, heparin-binding EGF- like growth factor as well as betacellulin; EGF, and TGF- $\alpha$  bind exclusively to EGFR.

The binding of a ligand to the EGFR initiates a cascade of events, the first of which is receptor dimerization, followed by autophosphorylation of receptor associated tyrosine kinases (intracellular carboxyl terminal region) which in turn become binding sites for SH2- containing signalling proteins. Dimerization consists of either homodimerization or heterodimerization between various members of the EGFR family of receptors. Signal transduction then proceeds, culminating in nuclear gene activation. Activated EGFR's are internalized and then either degraded or recycled, depending on the ligand bound to the receptor. Extensive cross talk and transactivation occurs between the members of the EGFR family, and EGFR is believed to be important in multiple signal transduction pathways. EGFR appears to play a critical role in both tumorigenesis and tumor growth, with its effects mediated by receptor overexpression, mutation of receptors with resulting constitutive activation or the presence of autocrine loops with resultant auto- stimulation. EGFR and its ligands have been shown to be overexpressed or to be involved in autocrine

growth loops in a number of tumor types, including NSCLC (Fujino 1996, Rusch 1997, Salomon 1995). It is known that overexpression of the EGF receptor in NIH3T3 cells confers a transformed phenotype if ligand for the receptor is present. Further, the expression of EGFR appears to correlate with radioresistance and lack of apoptosis of murine tumors expressing wild type p53. Increased EGFR expression is frequently noted in epithelial human tumors, most commonly due to gene amplification, but the increase in expression can also be mediated by increased transcription.

A number of different deletions of EGFR mRNA have been described, including 3 involving the extracellular domain; in type I the extracellular domain is deleted, the receptor cannot bind ligand, but is constitutively activated; type II contains a deletion in domain IV and remains capable of ligand binding and signal transduction; type III, the most common, lacks domains I and II, cannot bind ligand but is constitutively activated and is frequently overexpressed. Receptors that have undergone type III mutations are not internalized and may thus be overexpressed at the cell surface. A number of tumor types including non- small cell lung cancer (NSCLC) have been shown to express truncated EGFR ( Moscatello 1995). The truncated receptor, especially type III, may also arise through an alternate splicing mechanism in some tumors. The mutated receptor results in increased proliferation and decreased apoptosis in murine models and may confer drug resistance as well as altered sensitivity to some EGFR tyrosine kinase inhibitors. In addition to well- described growth stimulatory effects of EGFR activation (either by overexpression, mutation and constitutive activation or autocrine stimulation as described above), other effects have been described, such as the inhibition of apoptosis. Both EGF and TGF- $\alpha$  are known to induce angiogenesis, and promote invasion. As EGFR appears to play an important role in tumor growth, it has been widely investigated not only as a potential target, but also as a predictor of outcome for patients with early or late stage epithelial malignancies. An increase in EGFR expression appears to correlate with aggressive morphology and poor outcome in NSCLC (Pavelic 1993). Other investigators have demonstrated an association between EGFR expression and poor response to therapy (Volm 1992). Overall, EGFR is believed to play an important role in the development and progression of human epithelial malignancies and be a relevant target for chemotherapeutics.

Inhibitors of EGFR tyrosine kinase activity (EGFR TKIs) have been in development for a number of years, and while earlier compounds lacked specificity and potency, newer compounds have proven active in preclinical and early clinical studies and are now in late phase clinical development. Reversible inhibitors of EGFR currently include quinazoline-based compounds such as ZD1839, PD153035 and CP- 358,774 ( OSI-774), pyridopyrimidines ( PD158780) and pyrrolopyrimidines such as CGP 59326. The quinazoline- based compounds are the most advanced in clinical development.

#### 2.4 Rationale for This Study

The current standard therapy for patients with non- small cell lung carcinoma who have progressed despite combination chemotherapy regimens is single agent therapy with

docetaxel or other agents not given in first line chemotherapy regimens; some patients will not be suitable for second line regimens because of poor performance status or organ dysfunction. Patients who progress despite second line therapies, or who are not planned for or refuse second line therapy, are usually managed supportively and do not receive active cytotoxic therapy. The proposed study examines whether a novel EGFR TKI, OSI-774 (Tarceva), would improve survival in this group of patients. OSI-774 has shown evidence of antitumor activity in patients with NSCLC who have progressed despite platinum based chemotherapy (response rate 16%, 26% stable disease) (Perez- Soler 2001). A placebo- controlled group is proposed and is believed to reflect clinical equipoise as these patients would otherwise receive best supportive care as the standard of care. Randomization will be 2:1 so that 67% of patients will receive OSI-774, thus minimizing the number of patients receiving placebo.

Quality of Life (QoL) will be assessed in all patients. QoL is a particularly relevant outcome as these patients have limited survival, and whether or not their QoL is maintained (or even improved) becomes of great importance. Any possible survival gains from new therapies need to be assessed in terms of their QoL impact. If this drug is beneficial, QoL in treated patients should be better than QoL in patients on the placebo arm. Both arms may show a decline of QoL over time, due to the progressive deterioration in the clinical condition of these patients who will be late in their natural history, having already had first or second line chemotherapy. The toxicities associated with OSI-774 (rash, diarrhea) may negatively impact on the QoL of treated patients, or may not be of the type or severity that a QoL effect will be noticeable. Thus, a patient perspective of the impact of treatment is felt to be an essential part of this study. A well validated questionnaire is needed, and cultural and linguistic adaptation was deemed essential as this will be a multinational study with Canadian and international centres participating. Thus, the EORTC core QoL questionnaire (QLQ C30) and the lung cancer module (QLQ LC13) are being used.

## 2.5 Correlative Studies

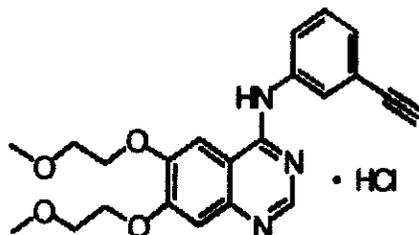
It is hypothesized that the expression of EGFR, activated EGFR (p-EGFR) and or activating mutations in EGFR may correlate with outcomes and response to therapy. If this proves to be the case, it may be feasible to better define a cohort of patients who are most suitable for therapy with agents such as OSI-774. All patients randomized to the trial, who consent to submission of tissue, will have tissue collected as paraffin embedded blocks. Tissue will be evaluated for the expression of EGFR, phosphorylated EGFR, p-ERK and the presence of common mutations in EGFR. All of these can be measured using readily available immunocytochemical assays. Other assays may be performed if considerate appropriate (Appendix VI)

In addition, plasma samples will be banked for all consenting patients. Planned analyses include EGFR, VEGF, and PDGF levels, as well as IL-1, IL-6, IL-8, TNF, IFN-g (Appendix VI and VIII).

**BACKGROUND THERAPEUTIC INFORMATION 3.1 OSI-774 (Tarceva)**

See the OSI-774 Investigator Brochure for additional details (OSI Investigator Brochure 2001).

**3.1.1 Chemical Structure**



Laboratory Code: OSI-774 ( free base)  
 OSI-774- 01 ( hydrochloride salt)  
 Molecular Formula: C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>

Molecular weight 393.4  
 Molecular weight 429.9

**3.1.2 Mechanism of Action** OSI-774 inhibits the human EGFR tyrosine kinase, with an IC<sub>50</sub> of 2 nM (0.786 ng/ mL) in an in vitro enzyme assay, and reduces EGFR autophosphorylation in intact tumor cells with an IC<sub>50</sub> of 20 nM ( 7.86 ng/mL). This inhibition is selective for the EGFR tyrosine kinase; both in assays assessing the effects of OSI-774 on a variety of other isolated tyrosine kinases, as well as in cellular bioassays designed to isolate this functional pathway.

**3.1.3 Experimental Antitumor Activity** The epidermal growth factor receptor (EGFR) is overexpressed in a significant percentage of these tumors. The mechanism of action of OSI-774 is direct inhibition of the EGFR tyrosine kinase. OSI-774 inhibits human EGFR tyrosine kinase with an IC<sub>50</sub> of 2 nM (0.79 ng/ ml) in an in vitro enzyme assay, and reduces EGFR autophosphorylation in intact tumor cells with an IC<sub>50</sub> of 20 nM (7.9 ng/ ml). This inhibition is selective for EGFR tyrosine kinase in assays of isolated tyrosine kinases and cellular assays. OSI-774 inhibits the EGF- dependent proliferation of cells at submicromolar concentrations and blocks cell cycle progression at the G1 phase. Oral administration of OSI-774 to mice reduces the level of EGFR autophosphorylation in human tumor xenografts by > 70% for over 12 h. Daily administration of OSI-774 markedly inhibits the growth of HN5 human head and neck tumor and A431 squamous epidermis carcinoma xenografts in athymic mice; nearly complete inhibition of tumor growth during a 20-day treatment regimen is obtained at the highest doses.

**3.1.4 Animal Pharmacokinetics and Toxicology**

In toxicology studies, the major effects attributed to OSI-774 involved the cornea, skin, ovaries, gastrointestinal system, liver, and kidney. Hematological changes, characterized by decreases in red cell parameters or increases in white blood cell numbers due to

increases in neutrophils, were also evident which were considered secondary to the effect on the kidney.

Treatment-related decreases in food consumption which may be secondary to a decrease in gastric emptying were observed in rats at 5, 15 and 35 mg/kg/day in a 2-week study and at 10 mg/kg/day in the 1-month study. Decreases in body weight gain were apparent at 15 and 35mg/kg/day in the 2 week study and at 5mg/kg in the 1 month study. Frequent emesis was observed in dogs dosed with 100 and 250 mg/kg/day prompting discontinuation of dosing beyond Day 3 and Day 2 respectively. Gastrointestinal changes in dogs dosed for 2 weeks at 50mg/kg/day included glandular dilatation in the duodenum, jejunum, ileum, caecum and rectum and inflammation in the esophagus.

In 2/3 male and 1/3 female dogs dosed at 50mg/kg/day for 1 month there was an increase in the number of regenerating proximal tubules in the kidney and affected tubules often contained necrotic debris. Papillary necrosis was observed in the rat 6-month study at doses of 5 mg/kg/day and in the dog when dosed at 50 mg/kg/day for 2 weeks as part of the 12 month study.

Hepatic changes were characterized by increases in aspartate and alanine transaminases in the rat and dog after dosing at 5mg/kg/day for 6 months in the rat and after 50mg/kg/day for 2 weeks in the dog. Hepatocellular necrosis was observed in the 6-month rat study at 10 mg/kg/day. Increases in bilirubin were also observed but it is possible that this change is a consequence of altered bilirubin metabolism mediated by UGT1A1 rather than a reflection of hepatic dysfunction. This is subject to further investigation.

Ovarian atrophy was observed at 5 mg/kg/day in the 6-month rat study. No such changes were observed in the 12 month dog study after dosing at 15mg/kg/day. Skin changes were characterized by hair follicular degeneration and inflammation observed in the rat 6-month study at doses  $\geq$  5 mg/kg/day and in the 12-month dog studies at doses  $\geq$  2.5 mg/kg/day. Skin reddening was also observed in an exploratory study in which cynomolgus monkeys were given oral doses ranging from 12.5 to 400mg/kg/day.

Ocular changes including corneal edema, ulceration, atrophy, and perforation were observed within 2 weeks in the 12-month dog study at 50 mg/kg/day. These changes fully resolved within 10 days of treatment discontinuation. Similar effects were not noted at the same dose in the 1-month dog study although pharmacokinetic data indicate that the dogs in the 12-month study had approximately 7 fold higher drug exposure than those in the 1-month study.

In toxicology studies, plasma concentrations increased with dose and increased plasma exposure (AUC) was generally correlated with increased toxicity. In the 1-month and 6 month studies in rat the no observed-adverse-effect level (NOAEL) was 1 mg/kg/day. The NOAEL in the 1-month dog study was 15 mg/kg/day. The NOAEL in the 12-month dog study was 7.5 mg/kg/day.

Following single dose dermal and ocular exposure in the rabbit OSI-774 was classified as being nonirritant upon ocular exposure to 54mg and afforded only minimal skin irritation in one animal dosed at 2000mg/ kg. Under the conditions of the guinea pig maximization test OSI-774 was classified as having mild potential for skin sensitization.

OSI-774 does not induce microbial or mammalian cell gene mutations in vitro, and does not produce chromosomal aberrations in vitro or in vivo.

### 3.1.5 Phase I Trials

To date, OSI-774 has been evaluated in over 300 patients in a number of phase I and II clinical studies. Clinical Protocol 248- 001 assessed the clinical pharmacology of OSI-774 in healthy male subjects given single oral solution/suspension doses of 1, 3, 10, 30, 100, 300, or 1000 mg. The most common adverse event in Protocol 248- 001 was headache. No clinically significant changes in ECGs, vital signs, hematology, clinical chemistry, liver function, or renal function tests were observed at any dose. When the oral powder for constitution was used, plasma concentrations of OSI-774 became quantifiable at 10 mg; systemic exposure increased with dose. Up to 300 mg, T<sub>max</sub> generally occurred between 0.5 and 3 h. At 1000mg, T<sub>max</sub> ranged from 1 to 18 h with a mean value of 6.8 h. Mean terminal phase half- lives ranged from 3 to 6 h for the 10 to 100 mg dose range and from about 10 to 11 h for the 300 and 1000 mg doses.

Protocol 248- 002 evaluated the clinical pharmacology of multiple oral dosing of 200 mg of OSI-774 BID for 14 days in healthy male subjects. Dermatitis was found on the face, neck, scalp, chest, and back of 6 of the 8 subjects (all 6 were on drug). Dosing was stopped for 1 subject after the 7th dose and for the remaining subjects after the 9th dose; the study was then terminated. Mild increases in total bilirubin, ALT, AST, leukocytes, lymphocytes, and neutrophils were observed. With the exception of 1 subject, clinical and blood chemistry parameters were within normal limits 14 days after discontinuing OSI-774. Exposure to OSI-420, an active metabolite of OSI-774, was < 10% of that for OSI-774.

Protocol 248-004 assessed the safety, tolerability, and pharmacokinetics of oral OSI-774 given daily to patients with advanced or refractory cancer. Adverse events were initially attributable to underlying disease, and were transient in nature. The protocol was therefore amended to allow patients with transient adverse events to continue on therapy, with more intensive monitoring. The protocol was further amended for the last dosing leg ( continuous daily dosing at 150 mg/ day, the maximum tolerated dose MTD) to enroll patients with EGFR- positive tumors and evaluate tumor metabolism via positron emission tomography ( PET). Mean plasma OSI-774 AUC 0-24 increased in a dose-related manner. The estimated accumulation following 21 days of once-daily doses of 100 mg was  $3.2 \pm 1.8$ . The observed accumulation following 21 days of once-daily doses of 150 mg was  $2.5 \pm 1.2$ .

Protocol 248- 005 assessed the safety, tolerability, and pharmacokinetics of oral OSI-774 given weekly on Day 1, 8, and 15 every 28 days at doses up to 1600 mg to patients with advanced or refractory cancer. At the 100 mg dose, no dose-limiting toxicities were observed; therefore, the protocol was amended to allow further dose escalation in 200 mg increments in subsequent cohorts of 3 subjects. These patients were required to have tumors that expressed the EGFR in order to maximize the potential for efficacy based on the drug's mechanism of action. This study completed enrollment without defining an MTD for OSI-774 given weekly. Mean AUC 0- 24 values suggest dose-related increases in exposure on day 8.

### 3.1.6 Pharmacokinetic Studies

Review of the pharmacokinetic profiles from protocols 248-005 and 248-004 revealed dose-related increases in exposure to OSI-774. Exposure to the active metabolite (OSI-420) represented approximately 10% of the parent compound, with an inter-subject variability in exposure of approximately two-fold. Repetitive daily dosing resulted in drug accumulation in some of the patients. The target average plasma concentration (Cav) of 500 ng/mL for clinical efficacy was achievable at doses at or above 100 mg in both the daily (protocol 248- 004) and weekly (protocol 248- 005) dosing studies. At the recommended dose of 150 mg/day, minimum plasma steady- state concentrations averaged 1.20 +/- 0.62 µg/mL, which is above the target concentration noted above. Other pharmacokinetic parameters determined from the daily dosing study included the clearance rate ( $6.33 \pm 6.41$  L/hour), elimination half-life ( $24.4 \pm 14.6$  hours), and volume of distribution ( $136.4 \pm 93.1$  L).

### 3.1.7 Rationale for the Dose and Schedule of OSI-774

The 150 mg daily dose of OSI-774 selected for all subsequent studies was based on pharmacokinetic parameters as well as the safety and tolerability profile of this dose level in phase I trials in advanced, heavily pre- treated cancer patients.

### 3.1.8 Phase II Studies

Protocol 248-101 assessed the safety, efficacy and tolerability of oral OSI-774 given daily at a dose of 150 mg to patients with advanced, refractory ovarian cancer. Secondary endpoints included duration of response, time to tumor progression, overall survival, one-year survival, monitor changes in CA- 125 and specific health- related quality of life measurements. These patients were required to have tumors that expressed the EGFR in order to maximize the potential for efficacy based on the drug's mechanism of action. Of the thirty-four patients enrolled, four partial responses (two unconfirmed) were documented and fourteen patients showed an indication of disease stabilization. Sixteen patients had progressive disease. The most commonly reported related adverse events were rash (67.6%) and diarrhea (38.2%), the incidence of which are consistent with previous studies.

Protocol A248-1003 is designed to assess the safety, efficacy and pharmacokinetics of oral OSI-774 given daily at a dose of 150 mg to patients with advanced, refractory head and neck cancer. Secondary endpoints to be evaluated include stable disease rates, time to progression, survival, and tumor-specific health-related quality of life measurements. As of July 2001 this study is on-going.

Protocol A248-1007 is designed to assess the safety, efficacy, and pharmacokinetics of oral OSI-774 given daily at a dose of 150 mg to patients with advanced, refractory non-small cell lung cancer. Secondary endpoints to be evaluated include stable disease rates, time to progression, overall survival, one- year survival and tumor-specific health-related quality of life measurements. These patients are required to have tumors that expressed the EGFR in order to maximize the potential for efficacy based on the drug's mechanism of action. As of July 2001 this study is on-going.

Emerging data from ongoing trials with OSI-774 suggests the possibility of a drug interaction when patients receive concurrent coumadin (warfarin). Approximately 400 patients have been treated to date on phase I, II or III trials with OSI-774, and of these patients, 7 have had increased INR reported while taking concomitant coumadin, sometimes necessitating changes in their dosage of coumadin. Both drugs are highly protein bound, and are metabolized via the Cyp3A4 pathway.

### 3.1.9 Pharmaceutical Data

OSI-774 is an off- white powder. The pharmaceutical preparations of OSI-774 are formulations containing the hydrochloride salt OSI-774-01). Unless otherwise stated, all preclinical and clinical evaluations were carried out using OSI-774-01; doses were based on free base equivalents. Initial clinical studies with OSI-774 used both a tablet and an oral powder for constitution (OPC) in water. Matching placebo will be supplied for this study.

Supplied: OSI-774/placebo will be supplied in bottles of 25mg, 100mg and 150mg tablets of the hydrochloride salt. Other size tablets (such as 50mg tablets) may become available during the conduct of the trial. . The amount dispensed will be sufficient supply to allow for 4 weeks ( 28 days) of consecutive once daily dosing, and provide for additional days of dosing, should the need arise.

Storage: Room temperature.

Route of administration: OSI-774/placebo is administered as a single daily oral dose (150mg, unless dose has been modified for toxicity). Prescribed daily dose is to be taken, preferably in the morning, with up to 200 mL ( ± 1 cup or 8 oz) of water. Drug should be taken at least 1 hour before or 2 hours after the ingestion of any food or other medications. Patients who are unable to swallow tablet and/ or who have silicon- based G- tubes may dissolve the tablets in distilled water.

**4.0 TRIAL DESIGN**

This is a randomized, double blind, placebo controlled phase III study of OSI-774 compared to placebo in patients with incurable stage IIIB/IV NSCLC who have failed at least one prior regimen, but no more than two prior regimens for advanced or metastatic disease.

**4.1 Stratification**

Patients will be stratified by:

- Centre
- Performance status ( ECOG) 0+1 vs. PS 2+3
- Best response to prior therapy ( CR or PR vs. SD vs. PD)
- Number of prior regimens ( one vs. two)
- Exposure to prior platinum ( prior platinum vs. no prior platinum)

**4.2 Randomization**

Patients will receive OSI-774 or placebo to a planned total sample size of 700.

Patients will be randomized to one of the following two arms:

Arm	Agent(s)	Total Dose	Route	Duration
A	OSI-774	150 mg	PO	Until unacceptable toxicity or progression
B	Placebo			

**5.0 STUDY POPULATION**

This is a randomized, double blind, placebo controlled phase III study of OSI-774 compared to placebo in patients with incurable stage IIIB/IV NSCLC who have failed at least one prior regimen, but no more than two prior regimens.

**5.1 Eligibility Criteria**

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed PRIOR to calling for randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to assure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients

with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Histologically or cytologically confirmed diagnosis of incurable stage IIIB/IV non-small cell carcinoma of the lung.

5.1.2 Patients must have evidence of disease but measurable disease is not mandatory (see section 10.2 for definitions of measurable disease). To be considered evaluable for complete or partial response assessment, patients must have at least one measurable lesion as follows: X-ray, ultrasound, physical exam  $\geq 20$  mm; Conventional CT scan  $\geq 20$  mm; Spiral CT scan  $\geq 10$  mm. Measurable lesions must be outside a previous radiotherapy field if they are the sole site of disease, unless disease progression has been documented at that site.

5.1.3 Male or female, 18 years of age or older.

5.1.4 With the exception of elderly patients, all patients must have received at least 1 combination chemotherapy regimen and must not be planned to receive further palliative cytotoxic chemotherapy. No more than 2 prior chemotherapy regimens is permissible (at least one of the two must have been a combination regimen). Elderly patients ( $\geq 70$  years of age) may have received 1 or 2 prior single agent regimens for their disease, in keeping with current standards of practice. Patients must have recovered from any toxic effects and at least 21 days must have elapsed from the last dose and prior to randomization (14 days for vinorelbine or other vinca alkaloids or gemcitabine).

5.1.5 Patients may have received prior radiation therapy providing that they have recovered from any toxic effects thereof and at least 7 days have elapsed between the last fraction and randomization.

5.1.6 ECOG performance status of 0, 1, 2 or 3

5.1.7 Adequate renal and hepatic functions as defined by the following required laboratory values obtained within 7 days prior to randomization: Serum creatinine  $< 1.5$  times the upper limit of normal; Total bilirubin  $< 1.5$  times the upper limit of normal; ALT (SGPT)  $< 2$  times the upper limit of normal. Note: If clearly attributable to liver metastasis, ALT (SGPT) values  $< 5$  times the upper limit of normal are permitted.

5.1.8 Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to randomization.

5.1.9 Patients must be able and willing to complete the quality of life questionnaires in a language for which validated translated questionnaires are available. The baseline assessment must already have been completed. Inability (illiteracy, loss of sight, or other

equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible. The baseline assessment must be completed within 7 days of randomization.

5.1.10 Patient consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements. It will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the NCIC CTG Study Coordinator that such clearance has been obtained, before the trial can commence in that centre. Because of differing requirements, a standard consent form for the trial will not be provided but a sample form is given in Appendix IX. A copy of the initial Full Board REB approval and approved consent form must be sent to the central office. The patient must sign the consent form prior to randomization or registration. Please note that the consent form for this study must contain a statement which gives permission for the NCIC CTG, OSI Pharmaceuticals or their designees (OSIP), and monitoring agencies to review patient records (see section 16.0 for further details).

5.1.11 Patients must be accessible for treatment and follow-up. Investigators must assure themselves that the patients randomized on this trial will be available for complete documentation of the treatment, toxicity, and follow-up.

5.1.12 All other investigations (as listed in section 6.0) have been performed prior to randomization.

5.1.13 In accordance with NCIC CTG policy, protocol treatment is to begin within 2 working days of patient randomization.

## 5.2 Ineligibility Criteria

Patients who fulfil any of the following criteria are not eligible for admission to the study:

5.2.1 History of breast cancer or melanoma at any time or history of another malignancy in the last 5 years. Patients with prior history of in situ cancer or basal or squamous cell skin cancer are eligible. Patients with other malignancies are eligible if they were cured by surgery alone and have been continuously disease free for at least 5 years.

5.2.2 Significant history of cardiac disease, i. e., uncontrolled high blood pressure, unstable angina, congestive heart failure, myocardial infarction within the previous year or cardiac ventricular arrhythmias requiring medication.

5.2.3 Serious active infection at the time of randomization or other serious underlying medical conditions that would impair the ability of the patient to receive protocol treatment.

5.2.4 Patients with known central nervous system metastases who are asymptomatic and on a stable dose of corticosteroids for at least 4 weeks prior to randomization are eligible. CT scan of the brain is NOT required unless there is clinical suspicion of CNS metastases.

5.2.5 Any condition (e. g., psychological, geographical, etc.) that does not permit compliance with the protocol.

5.2.6 Pregnant or lactating females.

5.2.7 Women of child bearing potential or sexually active males who are not employing adequate contraception (or practicing complete abstinence).

5.2.8 Any major surgery within 2 weeks prior to randomization.

5.2.9 Patients who have ocular inflammation or infection should be fully treated prior to entry to the trial. Any patients requiring ophthalmic surgery during the course of the trial will be withdrawn from the study. Patients who continue to wear contact lenses may have an increased risk of ocular adverse events. The decision to continue to wear contact lenses should be discussed with the patient's treating oncologist and ophthalmologist.

5.2.10 Patients with clinically significant ophthalmologic or gastrointestinal abnormalities, including: Severe dry eye syndrome; Keratoconjunctivitis sicca; Sjogren's syndrome; Severe exposure keratopathy; Disorders that might increase the risk for epithelium- related complications (e. g., bullous keratopathy, aniridia, severe chemical burns, neutrophilic keratitis); Uncontrolled inflammatory gastrointestinal diseases ( Crohn's, ulcerative colitis etc)

5.2.11 History of allergic reactions attributed to compounds of similar chemical or biologic composition to OSI-774.

5.2.12 Prior treatment with inhibitors of EGFR of any kind

5.2.13 Patients known to be HIV positive.

5.2.14 Patients who require oral anticoagulants (coumadin, warfarin) are eligible provided there is increased vigilance with respect to monitoring INR ( see sections 6.0 and 9.0). If medically appropriate and treatment available, the investigator may also consider switching these patients to LMW heparin, where an interaction with OSI-774 is not expected.

## 6.0 PRE- TREATMENT EVALUATION

## CLINICAL RUY

	Investigations	Timing: Days prior to randomization
History And Physical Exam including:	• Prior therapy, history, concomitant medications	
	• Physical examination 7 days	7 days
	• Height, weight, ECOG Performance Status • Clinical tumor measurements	
Hematology	• Hemoglobin	
	• White cell count, granulocytes	7 days
	• Platelet count	
	• INR <sup>7</sup>	
Biochemistry	• Total bilirubin	
	• Creatinine	
	• ALT	7 days
	• LDH	
	• Total Protein	
	• Albumin	
Radiology	• CXR	
	• CT scan of chest and upper abdomen	
	• CT scan of brain <sup>1</sup>	28 days <sup>2</sup>
	• Other scans as necessary to document all sites of disease	
	• EORTC QLQC30 + QLQ LC13	within 7 days
Quality of Life	prior to	
	randomization	
Other Investigations	• EKG	14 days
	• Collection of tissue blocks requested after	will be
	randomization	
Toxicity <sup>4</sup>	• Ophthalmology assessment <sup>5</sup>	7 days
	• Pregnancy test	72 hours <sup>3</sup>
	• Plasma sample for PK/AAG and correlative studies <sup>6</sup>	7 days
	Baseline toxicity evaluation (to document residual toxicity from previous therapy and baseline symptoms)	7 days

1. Only if clinical suspicion of metastases
2. Negative scans performed within 35 days of randomization need not be repeated. All patients should have baseline CT scans; if all disease is visible on CXR, CXR may be used to follow disease.
3. In women of childbearing potential only
4. Toxicities will be graded and recorded according to the NCI Common Toxicity Criteria Version 2.0 (Appendix V)
5. Ophthalmological assessment should be done at baseline only in patients who have symptoms suggestive of corneal disease and/or abnormalities. It should consist of a visual acuity test, examination for hyperemia, slit-lamp examination with fluorescein staining and Schirmer's test.
6. See appendix VI and VIII. May be done after randomization providing prior to treatment start date.
7. **Only for patients receiving coumadin at the time of randomization.**

## 7.0 ENTRY/ RANDOMIZATION PROCEDURES

### 7.1 Entry Procedures

All eligible patients enrolled on the study by a participating treatment centre will be entered into a patient registration log provided by the NCIC CTG. Centre codes for International ( non- Canadian) centres who have not previously participated in NCIC CTG studies will be assigned at the time of centre activation. Each centre will also be assigned a centre number to facilitate IVRS usage. In addition, centres should maintain screening logs of all patients screened for the trial.

All randomizations will be done centrally using an IVRS ( Interactive Voice Randomization System). Full details will be provided at the time of study activation. At the time of randomization, a copy of the completed eligibility checklist must be available.

Patient identification (NCIC CTG 2 letter centre code plus the last 3 digits of the patient number assigned by IVRS ) must be used on all documentation and correspondence with the NCIC CTG.

The following information will be required:

- patient's date of birth
- completed and signed eligibility checklist
- confirmation the patient meets all eligibility criteria
- exception number - IF granted
- stratification parameters

### 7.2 Stratification

The randomization procedure will dynamically minimize the imbalance between treatment arms within each of the following stratification factors:

Centre PS 0+1 vs. PS 2+3; best response to prior therapy ( CR or PR vs. SD vs. PD); number of prior regimens ( one vs. two); exposure to prior platinum ( prior platinum vs. no prior platinum)

### 7.3 Randomization

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis.

All randomized patients will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization. All randomized patients are to be followed until death.

## 8.0 TREATMENT PLAN

Although the National Cancer Institute of Canada Clinical Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with NCIC CTG policy, protocol treatment is to begin within 2 working days of patient randomization.

The terms "study drug" or "investigational product" refer to OSI-774/ placebo. The patient will be considered "on treatment" until all study drugs are discontinued. OSIP or designee will supply all study drugs.

### 8.1 Treatment Plan

The first dose of OSI-774/placebo must be given within 2 working days after randomization. The treatment code for OSI-774 will be double blind, meaning that neither the investigator nor the patient will have knowledge of the treatment arm assigned. Active or placebo OSI-774 will be assigned via IVRS (see section 7.0). NCIC CTG and OSIP personnel, including those involved in the monitoring, data management or data analysis will not have access to the treatment code during the conduct of the trial.

No dose escalation of OSI-774/placebo is permitted. OSI-774/placebo will be reduced for toxicities as detailed in section 8.5. Toxicity will be graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 (CTC v. 2.0). Treatment with OSI-774/ placebo may be delayed for no more than three weeks to allow recovery from toxicity.

**Drug Administration**

Arm	Agent(s)	Dose	Route	Schedule
A	OSI-774	150 mg	PO	Daily <sup>1</sup>
B	Placebo	150 mg	PO	Daily <sup>1</sup>

<sup>1</sup> Until progression. In the absence of unacceptable toxicity

**8.2 OSI-774/ placebo**

OSI-774 and matching placebo are identical in appearance as are the bottles in which they are provided. The bottles of active and placebo OSI-774 will each be labeled with a three- panel, double blind label. The sealed part of the label will be affixed to the Drug Accountability CRF page following dispensing.

Blinding is critical to the integrity of this clinical drug trial. However, in the event of a medical emergency in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken. Before requesting breaking of the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i. e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product- related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding. The need to break the blind must be discussed with the NCIC CTG and the best method to do this will be determined. For unblinding outside normal working hours call 613- 548- 3232 and ask for the pharmacist- on- call for emergency unblinding (Kingston General Hospital, Kingston, Ontario, Canada). For any treatment code unblinding, the reason and parties involved must be documented in the patient's medical record.

Treatment identification information should be kept confidential and should be disseminated only to those individuals that must be informed for medical management of the patient.

**8.3 Premedication**

No routine premedication will be given for OSI-774/placebo. Nausea has been commonly observed (~ 50%) and is usually transient in nature. Routine premedication for nausea is not believed necessary, but symptomatic patients should be treated with standard anti-nausea/ antiemetic therapy as necessary.

**8.4 Drug Administration**

OSI-774/ placebo will be given at a fixed dose of 150 mg as a single daily oral dose. Dosage is not based upon body weight or body surface area. Prescribed daily dose is to

be taken preferably in the morning, with up to 200 ml of water. Drug should be taken at least 1 hour before or 2 hours after the ingestion of any food or other medications, including grapefruit juice, vitamins and iron supplements. Patients who are unable to swallow tablet and/ or who have silicon- based G- tubes may dissolve the tablets in distilled water as described below for G- tubes.

Administration through G- tube: The tablets required for the dose should be dissolved in 100 ml of sterile water. The dissolved tablets should be shaken vigorously to form a uniform suspension. The suspension should be drawn up into a syringe and administered through the G- tube port. Repeat the syringe transfer until the entire volume has been administered. A small volume ( 40 ml) of sterile water should be added to the container used to dissolve the tablets and the residual suspension should be shaken, aspirated into the syringe, and administered. This last step should be repeated to ensure the entire dose is administered. The total volume of delivery/ rinse is approximately 180ml.

OSI-774/ placebo will be administered on an outpatient basis.

Missed daily doses should be skipped. Doses should be taken at the same time each day. If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted. If a patient misses a dose normally taken in the morning, s/ he may take the dose any time during that same day. However, the missed dose should not be taken on a subsequent day. Patients will be instructed to notify study site personnel of missed doses.

### 8.5 Dose Adjustments

Doses will be reduced for hematologic and other toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI Common Toxicity Criteria Version 2.0 ( see Appendix V).

The major toxic effects of OSI-774 are diarrhea and skin rash. Other reported side effects include fatigue, dry skin, pruritus, anorexia, nausea, vomiting, dry mouth, dry eye and headache. The guidelines, which follow, outline dose adjustments for several of these toxic effects. If a patient experiences several toxicities and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

In the event of toxicity ( e. g., diarrhea, rash) that is: Not controlled by optimal supportive care, or Not tolerated due to symptomatology, disfigurement, or interference with normal daily activities, regardless of severity then the daily dose of OSI-774 will be decreased according to the schedule displayed in the following table. If significant toxicity is still apparent, the dose may be reduced a second time. Dose reductions may take place whenever toxicity is noted during the study.

Starting Dose

First Reduction

Second Reduction

(mg/day)  
150

(mg/day)  
100

(mg/day)  
50

**APPEARS THIS WAY  
ON ORIGINAL**

**Dose Reduction criteria and guidelines for management of OSI-774 related toxicities**

Toxicity	Grade	Guideline for management	OSI-774 dosage modification*
Keratitis	1	No intervention	None
	2	Preservative-free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks	If $\geq 2$ weeks in duration, hold until recovery to $<$ grade 1 And then Reduce 1 dose level
	$\geq 3$		Hold until recovery to $<$ grade 1 And then Reduce 1 dose level
Diarrhea	1	No intervention	None
	2	Loperamide (4 mg at first onset, followed by 2 mg every 2-4 hrs until diarrhea free for 12 hrs)	None **
	$\geq 3$ (despite optimal use of loperamide)		Hold until recovery to $<$ grade 1 And then Reduce 1 dose level
Rash	1	No intervention	None

	2	Any of the following: minocycline <sup>†</sup> , topical tetracycline or clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)	None **
	≥ 3		Hold until recovery to < grade 1 And then Reduce 1 dose level
Signs and symptoms of Interstitial Pneumonitis		Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated.	Hold pending diagnosis. Permanently discontinue if diagnosis is confirmed and considered possibly related to OSI-774.
Other toxicity	≥ 2 prolonged clinically significant toxicity	Treatment as appropriate	Hold until recovery to < grade 1 And then Reduce 1 dose level

\* if no recovery after 21 days of holding drug, patients should go off study

\*\* if dose has been previously held for grade 2 rash or diarrhea, and grade 2 symptoms recur, OR if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then reduce dose one level

+ recommended dose: 200mg po bid (loading dose), followed by 100mg po bid for 7-10 days

Patients experiencing toxicities that require a delay in scheduled OSI-774 dosing for > 21 days will be discontinued from further participation in this study. When a dose reduction is required, no dose reescalation will be permitted for the duration of study treatment.

### 8.6 Duration of Therapy

Patients will receive OSI-774 or placebo daily beginning Day 1 and continue until unacceptable toxicity or disease progression.

### 8.7 Patient Compliance

Daily therapy with OSI-774 is considered important to maximizing potential benefit from this class of compounds. Study site staff will make pill counts approximately every 4 weeks. Dates of missed or modified doses will be recorded in the CRF. Intermittent trough levels of OSI-774 will be taken in all patients to document compliance and to determine whether there is any association between levels and patient outcomes (adverse events, survival, etc.) (Appendix VIII). Details of sample collection and shipping are provided in Appendix VIII.

### 8.8 Supportive Care Guidelines

**Diarrhea:** Diarrhea has been commonly observed (~ 50%) and is usually transient in nature. Previous trials have shown that the frequency and severity of diarrhea rarely

hindered administration of OSI-774 and could be managed with loperamide. The recommend dose is loperamide 4 mg at first onset, followed by 2 mg q 2- 4 hr until diarrhea free for 12 hr.

Rash: Skin rash or dermatosis (grade 1- 2) has been observed during the first several days of treatment with OSI-774 in many patients (~ 50%) and has been observed to diminish in severity despite continued treatment in many patients. In some patients, this rash appeared to be treatable with standard acne therapies, including topical and oral antibiotics used to treat acne. Anecdotal reports of improvement have occurred with several agents . In patients with severe rash, treatment may need to be discontinued or the dose reduced (see section 8.5 for details).

### 8.9 Concomitant Therapy

8.9.1 Permitted Patients may receive low dose, non- myelosuppressive palliative radiation therapy if required (contact NCIC CTG if interpretation is required). Patients who have evidence of disease progression requiring radiation therapy should discontinue protocol treatment. Patients who develop brain metastases as their sole site of disease progression while on study may stay on study drug providing there is evidence of systemic control or response, and the investigator judges this is in the patients best interests. NOTE: the date of disease progression remains the date of the new lesions, even though the patient remains on study.

Patients should receive full supportive care during the trial, including transfusion of blood products, and treatment with antibiotics, antiemetics, antidiarrheals and analgesics when appropriate.

Patients with dry eyes (an abnormal Schirmer's test results on baseline eye exam) should be advised to use an ocular lubricant.

Concomitant treatment with coumadin is permitted provided increased vigilance occurs with respect to monitoring INR ( see section 9.0).

### 8.9.2 Not Permitted

Colony stimulating factors should not be used prophylactically or in place of a scheduled dose reduction.

Administration of any other anti-cancer therapy (cytotoxic, biological/ immunotherapy or full dose radiotherapy) is not permitted until after disease progression is documented. Thereafter patients may be treated at the investigators discretion.

Patients who receive study drug should not receive ANY other (non-anti-cancer) investigational drugs until after the post-treatment assessment (at least 30 days after the final dose of any study drug).

Patients who continue to wear contact lenses may have an increased risk of ocular adverse events. The decision to continue to wear contact lenses should be discussed with the patient's treated oncologist and ophthalmologist.

### 8.9.3 Potential for Drug Interactions

In *in vitro* human liver microsomes studies OSI-774 was slowly oxidized. OSI-774 appeared to be a substrate for CYP3A4, suggesting that OSI-774 could reduce the clearance of co-administered drugs whose metabolism is dependent on these P450 cytochrome isoenzymes. In addition, OSI-774 pharmacokinetics may be influenced by co-administration of drugs with effects on CYP3A4. Physicians should be aware if patients are on these medications and should monitor patients if relevant or appropriate (see Appendix X).

The possibility of a drug interaction between OSI-774 and coumadin exists and is based on the highly protein bound nature of both drugs and/ or alteration of CYP 450 activity (see section 3.1) Increased surveillance of coagulation parameters (INR) in all patients receiving coumadin while on study is mandated ( see sections 6.0 and 9.0).

## 9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

### 9.1 Evaluation During Protocol Treatment

During protocol treatment with OSI-774/ placebo each cycle is 28 days (4 weeks) in length.

Investigations	Timing
History and Physical Exam including:	
<ul style="list-style-type: none"> <li>• Concomitant medications</li> <li>• Physical examination</li> <li>• Weight, ECOG Performance Status</li> <li>• Clinical tumor measurements<sup>1</sup></li> </ul>	every 4 weeks on day 1 of each cycle
Hematology	
<ul style="list-style-type: none"> <li>• Hemoglobin</li> <li>• White cell count, granulocytes</li> <li>• Platelet count</li> <li>• INR<sup>a</sup></li> </ul>	every 4 weeks on day 1 of each cycle
Biochemistry	
<ul style="list-style-type: none"> <li>• Total bilirubin</li> <li>• Creatinine</li> <li>• ALT</li> <li>• LDH</li> <li>• Total Protein</li> <li>• Albumin</li> </ul>	every 4 weeks on day 1 of each cycle

Pharmacokinetics and correlative studies	<ul style="list-style-type: none"> <li>• OSI-774 /AAG levels</li> <li>• Plasma sample<sup>2</sup></li> </ul>	every 4 weeks on day 1 of each cycle <sup>3</sup>
Radiology	<ul style="list-style-type: none"> <li>• CXR</li> <li>• CT scan of chest<sup>4</sup></li> <li>• Other scans as necessary to document all sites of disease<sup>5</sup></li> </ul>	every 8 weeks at the end of every 2 cycles
Quality of Life	<ul style="list-style-type: none"> <li>• EORTC QLQC30 + QLQ LC13 subscale</li> </ul>	every 4 weeks on day 1 of cycle 2 and each subsequent cycle
Other Investigations	<ul style="list-style-type: none"> <li>• EKG<sup>6</sup></li> </ul>	every 8 weeks
Toxicity <sup>7</sup>	Toxicity evaluation	each visit

1 Every 8 weeks at the end of every 2 cycles.

2 See appendix VI and VIII.

3 Should be taken prior to the dose of OSI-774 that day where possible (Appendix VIII).

4 Include upper abdomen if evidence of disease in baseline upper abdominal scan. If all disease is visible on a plain CXR, patients may be followed by CXR.

5 Bone scans do not need to be repeated routinely except to confirm CR or PR (mandatory) or as clinically indicated.

6 Only if clinically indicated.

7 Toxicities will be recorded and graded according to the NCI Common Toxicity Criteria Version 2.0 (Appendix V).

8 Only for patients receiving coumadin. To be done twice a week, weekly for 3 weeks; then weekly or more often as clinically indicated.

**Evaluation After All Protocol Treatment Has Been Discontinued**

	Investigations	Timing – 12 Weekly
History and Physical Exam including:	<ul style="list-style-type: none"> <li>• Physical examination</li> <li>• Weight, ECOG Performance Status</li> <li>• Concomitant medications</li> <li>• Clinical tumor measurements<sup>1</sup></li> </ul>	each visit at 4 week visit only until progression
Hematology	<ul style="list-style-type: none"> <li>• Hemoglobin</li> <li>• White cell count, granulocytes</li> <li>• Platelet count</li> <li>• INR<sup>8</sup></li> </ul>	at 4 week visit only

Biochemistry	<ul style="list-style-type: none"> <li>• Total bilirubin</li> <li>• Creatinine</li> <li>• ALT</li> <li>• LDH</li> <li>• Total Protein</li> <li>• Albumin</li> </ul>	at 4 week visit only
Radiology <sup>1</sup>	<ul style="list-style-type: none"> <li>• CXR</li> <li>• CT scan of chest</li> <li>• Other scans as necessary to document all sites of disease<sup>5, 6</sup></li> </ul>	until progression
Quality of Life	<ul style="list-style-type: none"> <li>• EORTC QLQC30 and QLQ LC13 progression<sup>7</sup></li> </ul>	at 4 week visit and until
Other Investigations	<ul style="list-style-type: none"> <li>• EKG<sup>2</sup></li> <li>• Plasma sample<sup>8</sup></li> </ul>	at 4 week visit only
Toxicity <sup>4</sup>	Toxicity Evaluation	each visit

1 Only required until disease progression is documented.

2 Only if clinically indicated.

3 Women of childbearing potential only.

4 Toxicities will be recorded and graded according to the NCI Common Toxicity Criteria Version 2.0 (Appendix V). New

or ongoing toxicity that is definitely, probably or possibly related to protocol treatment only.

5. Include upper abdomen if evidence of disease at baseline in upper abdominal scan. If all disease is visible on a plain

CXR, patients may be followed by CXR.

6. Bone scans do not need to be repeated routinely except to confirm CR or PR (mandatory) or as clinically indicated.

7. To be completed until PD. At least one Questionnaire should be completed by all patients.

Patients must complete their

final Questionnaire within 2 weeks of PD. If off treatment for PD, and QoL already completed within 2 weeks of date of

PD, Questionnaire need not be completed at 4 week visit.

8. See appendix VI and VIII.

9 Only for patients receiving coumadin.

The following plan should be followed once treatment with OSI-774/ placebo is discontinued.

## 10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

### 10.1 Definitions

10.1.1 Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first dose of protocol therapy.

10.1.2 Evaluable for response. All patients who have measurable lesions (see below) and who have at least one objective tumor assessment after baseline will be considered

evaluable for response unless early progression is documented in which case they will be also be considered response-evaluable. Patients will have their response classified according to the definitions set out below.

10.1.3 **Evaluable for Quality of Life Assessment** All patients who have completed quality of life assessments are evaluable for quality of life

10.2 **Response and Evaluation Endpoints**

Response and progression will be evaluated in this study using the new international criteria proposed by RECIST ( Response Evaluation Criteria in Solid Tumors) committee (Therasse et al 2000). Changes in only the largest diameter ( unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

10.2.1 **Measurable Disease.** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as <20 mm with conventional techniques (PE, CT, XR, MRI) or as <10 mm with spiral CT scan. All tumor measurements must be recorded in millimetres (or decimal fractions of centimetres).

10.2.2 **Non- measurable Disease.** All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/ pericardial effusions, lymphangitis cutis/pulmonis ( skin/pulmonary), inflammatory breast disease, abdominal masses (not followed by CT or MRI) and cystic lesions are all non-measurable.

10.2.3 **Target Lesions.** All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response. If there are > 10 measurable lesions, those not selected as target lesions will be considered together with non-measurable disease as non-target lesions (see 10.2.4).

10.2.4 **Non- target Lesions.** All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 10 listed as target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

10.3 **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 tumor (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	
Any	PD	Yes or No	PD	No prior SD, PR or CR
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.

#### 10.4 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.

#### 10.5 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.

#### 10.6 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.

**10.6.1 Clinical Lesions.** Clinical lesions will only be considered measurable when they are superficial (e. g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

**10.6.2 Chest X- ray.** Lesions on chest X- ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

**10.6.3 CT, MRI.** CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

**10.6.4 Ultrasound.** When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements for superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

**10.6.5 Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centres. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

**10.6.6 Cytology, Histology.** These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

## **11.0 ADVERSE EVENT REPORTING**

### **11.1 Definition of a Serious Adverse Event Requiring Expedited Reporting**

All serious adverse events must be reported in an expedited manner ( see section 11.2 for reporting instructions).

A serious adverse event ( SAE) is any adverse event that at any dose:

Results in death (grade 5 event) Is life- threatening Requires inpatient hospitalization or prolongation of existing hospitalization Results in persistent or significant disability or incapacity Is a congenital anomaly/ birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately lifethreatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

Hospitalizations for routine procedures, investigations, and palliative care or pain control are NOT considered a Serious Adverse Event in this protocol.

### **11.2 Serious Adverse Event Reporting Instructions**

All protocol defined serious adverse events, occurring within 30 days of the last dose of investigational product, irrespective of relationship, must be reported in an expedited manner as follows:

Canada : Within 1 working day: Report event by telephone and/ or fax to: Dr. Lesley Seymour Phone 613- 533- 6430 or Aleksandra Trajkovic Fax: 613- 533- 2991 or Dianne Johnston NCIC Clinical Trials Group

Within 2 working days: Fax completed NCIC CTG Serious Adverse Event Form

Within 10 days: Mail completed Final NCIC CTG Serious Adverse Event Form

International Centres: Within 1 working day: Report event by telephone and/ or fax to: Regional Medical Monitor ( contact details to be provided at activation)

Within 2 working days: Fax completed NCIC CTG Serious Adverse Event Form to Regional Medical Monitor

Within 10 days: Fax completed Final NCIC CTG Serious Adverse Event Form

The Regional Medical Monitor will be responsible for forwarding all Serious Adverse Events to OSIP within 24 hours of receipt.

All serious adverse events, INCLUDING those reported in an expedited fashion must also be recorded on the Case Record Form.

### 11.3 Reporting Second Malignancies

Second malignancies or myeloid dysplasia must be reported in writing on a Serious Adverse Event Form within 15 working days of when diagnosis is known to the investigator.

### 11.4 Reporting Serious Adverse Events to Local Ethics Boards

Canada: NCIC CTG will notify Canadian Investigators of all Serious Adverse Events, which are reportable to regulatory authorities in Canada. This includes all serious events, which are unexpected and related to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Investigator Drug Brochure. Documentation from the REB of receipt of these reportable serious adverse events must be kept on file in the centre.

International Centres: OSIP will notify all Investigators (via Regional Medical Monitors) of all Serious Adverse Events which are reportable to regulatory authorities from this as well as other trials. This includes all SAEs which are reportable to regulatory authorities and which are unexpected and related to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Investigator Drug Brochure. Documentation from the REB of receipt of these reportable serious adverse events must be kept on file in the centre.

### 11.5 NCIC CTG Reporting Responsibilities

NCIC CTG will notify the Therapeutic Products Directorate of the Canadian Health Protection Bureau in an expedited manner of Serious Adverse Events, which are unexpected and related to protocol treatment, occurring on this trial, as well as reportable SAEs from other clinical trials reported to them by OSIP. NCIC CTG will immediately (within 1 working day of receipt at NCIC CTG) notify OSIP of all Serious Adverse Events from Canadian centres. Regional Medical Monitors will be responsible for reporting International SAEs to OSIP.

### 11.6 OSIP / Designee Reporting Responsibilities

OSIP will be responsible for notifying NCIC of IND safety updates and serious adverse events from other clinical trials, which have been reported to other regulatory authorities. OSIP / designee will notify non- Canadian regulatory authorities in an expedited manner

of Serious Adverse Events, which are unexpected and related to protocol treatment, occurring on this trial, as well as reportable SAEs from other clinical trials.

## **12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING**

### **12.1 Criteria for Discontinuing Protocol Treatment**

Patients may stop protocol treatment in the following instances:

12.1.1 Intercurrent illness, which would, in the judgment of the investigator, affects assessments of clinical status to a significant degree, and requires discontinuation of protocol therapy.

12.1.2 Unacceptable toxicity as defined in section 8.5.

12.1.3 Tumor progression or disease recurrence as defined in section 10.3.

12.1.4 Request by the patient.

12.1.5 Pregnancy.

### **12.2 Therapy After Protocol Treatment is Stopped**

Treatment after disease progression has been documented and all protocol therapy has been discontinued is at the discretion of the investigator.

### **12.3 Follow- up Off Protocol Treatment**

Refer to section 9.2 and Appendices I and IV for details of follow up and required investigations.

Efforts should be made to maintain the investigations schedule and continue follow- up, even if patients discontinue protocol treatment prematurely and/ or no longer attend the participating institution.

## **13.0 CENTRAL REVIEW PROCEDURES**

Central review of reported responses may be undertaken. Centres should maintain archival copies of all relevant imaging procedures utilized to assess response during the course of this trial, preferably with the study files for each of review.

## **14.0 STATISTICAL CONSIDERATIONS**

### **14.1 Introduction**

This is a randomized, double blind, placebo controlled study of OSI-774 in patients with non- small cell lung cancer who have failed at least one prior regimen, but no more than two prior regimens, for advanced or metastatic disease. Patients will be randomized to receive either OSI-774 ( ARM A) or placebo ( ARM B) in a 2: 1 ratio. Patients will be stratified by centre, performance status ( 0+1 vs. 2+3), best response to prior therapy (CR or PR vs. SD vs. PD), number of prior regimens (1 vs. 2) and exposure to prior platinum (Yes vs. No) by using the dynamic minimization method. The primary objective is to assess the effect of OSI-774 by comparing overall survival between ARM A and ARM B among all randomized patients. The progression free survival, response rate, time to response, duration of response, toxicity and quality of life between the two treatment arms will be compared. The correlation of expression of tissue EGFR levels at diagnosis to outcomes and response will be assessed. Additional correlative studies on tissue and plasma will be assessed in an exploratory fashion. Trough levels of OSI-774 will also be correlated with adverse events and response to treatment.

#### 14.2 Sample Size and Power

The sample size for this study is determined to compare overall survival between patients randomized to ARM A and patients randomized to ARM B. The median survival of patients on the placebo arm was estimated to be 4 months. In order to have 90% power to detect a 33% improvement with OSI-774 (i. e., from 4 months to 5.3 months, which corresponds a hazard ratio of 1.33), using a two- sided 5% level test of significance, we need to observe 582 deaths before the final analysis. Assuming that we would enter a total of 50 patients a month, the required number of deaths (582) would be observed by accruing 700 patients over 14 months and following all of them for at least 6 months after accrual is closed. The final analysis will be performed when 582 deaths are observed. The total duration of the trial is estimated to be around 20 months.

#### 14.3 Endpoints and Analyses

Overall survival, which is defined as the time from the randomization to the death of any cause, is the primary endpoint of this study. Patients who are alive at the time of final analysis will be censored at their last contact date. All randomized patients will be included in the analysis of overall survival. A Kaplan- Meier curve for proportions of survival in each treatment arm will be displayed. The 95% confidence intervals for the median survival will be computed using the method of Brookmeyer and Crowley. In the primary analysis, the two treatment arms will be compared using the log- rank test stratified by all stratification factors except centre plus patient's EGFR status ( positive/ mutated vs. unknown vs. negative) at baseline. In addition, the effect of study centre and other potential prognostic factors on overall survival will be assessed using Cox regression. The Schoenfeld residual plots will be used to check the model assumption for the Cox regression.

Progression free survival (PFS) is one of the secondary endpoints. It is defined as the time from randomization to the first observation of disease progression or death due to any cause. A patient who stops treatment with study drug and goes on to receive alternative therapy for NSCLC, prior to documentation of disease progression, will be censored on the date alternative therapy began. If a patient has not progressed or received alternative therapy, PFS will be censored on the date of the last disease assessment. All analyses for overall survival will be similarly performed for progression free survival.

Patients will be evaluable for objective tumor response if they have at least one measurable lesion at baseline and have at least one disease assessment after baseline. In addition, patients who develop PD prior to this time will also be considered evaluable for response. The response rate will be estimated as the proportion of patients evaluable for response who meet the criteria of complete or partial response. A Cochran-Mantel-Haenszel test will be used to compare tumor response rate between arms adjusting all stratification factors except centre plus patient's EGFR status (positive/ mutated vs. unknown vs. negative) at baseline.

Duration of response will be calculated for all patients achieving a PR or CR. Duration of PR/ CR is defined as the time from first objective status assessment of CR/PR to the first time disease progression is documented or death among those who have achieved a PR or CR. A patient who stops treatment with all study drugs and goes on to receive alternative therapy for NSCLC, prior to documentation of disease progression, will be censored on the date alternative therapy began. The date of progression will still be considered as the event date for the duration of response. If a patient has not progressed or died, the duration of response will be censored on the date of the last known alive date. Duration of response will be analysed using the similar methods described for overall survival.

The quality of life of patients will be assessed using EORTC QLQC30 (Aaronson, 1993) and the lung cancer module (QLQ LC13). The EORTC QLQC30 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 will be applied to standardize the raw score to range between 0 and 100. The QLQ-LC13 lung cancer module (Bergman et. al. 1994) 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 validity and reliability have been studied by the EORTC Study Group on Quality of Life. The EORTC QLQ-C30 and module will be scored according to the EORTC QLQ-C30 Scoring Manual, and analyzed accordingly. Since quality of life will be assessed longitudinally the method of analysis of variance for repeated measures will be used for domains represented by aggregate scores.

All patients who receive at least one dose of OSI-774/ placebo will be included in the safety analysis. Descriptive summary tables will be presented on safety parameters by

treatment arm. Toxicity rates will be compared between treatment arms using the Fisher's Exact Test or Chi-square test, as needed. There will be safety monitoring by the NCIC CTG Data Safety Monitoring Committee (DSMC) every 6 months.

Safety and efficacy data will be correlated with compliance as documented by pill counts recorded on the CRF. Population pharmacokinetic analyses and correlations with survival, responses, and adverse events will also be performed.

#### 14.4 Interim Analyses

No interim analysis for this study is planned.

### 15.0 PUBLICATION POLICY

#### 15.1 Authorship of Papers, Meeting Abstracts, Etc

15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

The first author will generally be the chair of the study.

In the event of a separate paper dealing with Quality of Life outcomes, the first author will generally be the Quality of Life coordinator;

A limited number of the members of the NCIC Clinical Trials Group and OSIP may be credited as authors depending upon their level of involvement in the study.

Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.

15.1.2 In an appropriate footnote or at the end of the article the following statement will be made:

" A study coordinated by the Clinical Trials Group of the National Cancer Institute of Canada. Participating investigators included: ( a list of the individuals who have contributed patients and their institutions)."

#### 15.2 Responsibility for Publication

It will be the responsibility of the study chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of

study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

### 15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the NCIC CTG physician and study coordinator, and approval of the study chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

## 16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

### 16.1 Institution Eligibility for Participation

All member centres in good standing of the NCIC CTG are eligible to participate in this study. International institutions, which are not NCIC CTG members, can either make application for membership or submit a single study agreement document.

### 16.2 Retention of Patient Records and Study Files

The Therapeutic Products Directorate of the Health Protection Branch states in its Guidelines of Clinical Investigations ( 1989) the following instructions with regard to retention of study records: " The responsible clinical investigator should maintain all records relating to the study for at least two years after the termination of the study. Up to the time of marketing, every reasonable attempt should be made by the responsible clinical investigator to retain records enabling the tracing of subjects that have received investigational new drugs. It is the responsibility of the sponsor to retain all records relating to the study."

The investigator must retain investigational product disposition records, copies of CRFs ( or electronic files), and source documents for the maximum period required by applicable regulations and guidelines ( which for the USA states that records should be retained for two years after a marketing application is approved) or institution procedures, or for the period specified by OSIP, whichever is longer. The investigator must contact OSIP prior to destroying any records associated with the study. OSIP will notify the Investigator when the trial records are no longer needed.

### 16.3 Regulatory Requirements

All Canadian investigators must complete a HPB 3005. International investigators will complete necessary regulatory documents as advised.

All investigators and subinvestigators must also complete financial disclosure forms that will be provided by NCIC CTG.

#### 16.4 REB (Research Ethics Board) Approval for Protocols

Each participating centre will have on file with the NCIC CTG central office, as part of its membership/ agreement documents, a description of its ethics review process.

Initial Approval Member centres wishing to participate in a trial are required to obtain full board local ethics approval of the protocol and consent form (see below) by the appropriate REB. In addition, a completed NCIC CTG Confirmation of Initial Ethical Approval form must be submitted to document the REB was properly constituted and there were no conflicts of interest in the REB approval process.

Annual Re- Approvals Annual re- approval is required for as long as the trial is open to patient accrual or patients are receiving protocol treatment or undergoing protocol-mandated interventions.

Amendments/ Revisions All amendments or revisions to the protocol must undergo review by local REBs. Amendments/ revisions will be circulated to all participating sites in a standard format with clear instructions regarding REB review. If full board approval of an amendment is required it will be specified.

#### 16.5 Informed Consent

Informed Consent Document The REB of an institution must approve the consent form document, which will be used at that centre prior to its local activation; changes to the consent form in the course of the study will also require REB approval.

It is essential that the consent form contain a clear statement, which gives permission for: 1) information to be sent to; and 2) source medical records to be reviewed by the NCIC CTG and other agencies as necessary. In addition, the consent form should include all ICH- GCP consent elements.

Consent Process/ Patient Eligibility Patients who cannot give informed consent ( i. e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

#### 16.6 Centre Performance Monitoring

Ineligibility and timeliness of data submission are monitored for all centres and the results are reported in the Centre Performance Index. This index is generated twice a year and there are minimum standards for performance.

Centres are required to submit Eligibility Checklist/ Form 1 ( Initial Evaluation), Form 3 ( Systemic Therapy Report and Form 5 ( Follow- up Reports) within the time guidelines specified in Appendix IV ( Documentation for Study).

#### 16.7 On- Site Monitoring/ Auditing

In addition to the routine review of case report forms and supporting documents sent to the central office, NCIC CTG site monitoring may be conducted at participating centres in the course of the study as part of the overall quality assurance programme. The auditors will require access to patient medical records to verify the data. On site monitoring will be conducted by NCIC CTG and OSIP ( or their designees) for this study.

#### 16.8 Case Report Forms

A list of forms to be submitted as well as expectation dates are to be found in Appendix IV.

#### 17.0 REFERENCES

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Prestudy	4-weekly	4 weeks F/U after off treatment)	12-Weekly
History, physical exam	X	X	X	X
Concomitant medications	X	X	X	
Clinical tumour measurement <sup>5</sup>	X	X <sup>2</sup>	X <sup>5</sup>	X <sup>5</sup>
ECOG PS	X	X	X	
Hemoglobin				
White cells, granulocytes				
Platelets	X	X	X	
INR <sup>11</sup>				
Total bilirubin	X	X	X	
Creatinine				
ALT				
LDH				
Total Protein				
Albumin				
CXR				
CT Chest <sup>8</sup>	X	X <sup>2</sup>	X <sup>5</sup>	X <sup>5</sup>
Other scans to document all sites of disease <sup>9</sup>				
QoL (EORTC QLQC30 + QLQ LC13) <sup>6</sup>	X	X <sup>1</sup>	X <sup>6</sup>	X <sup>6</sup>
EKG	X	X <sup>3</sup>	X	
Pharmacokinetics / Alpha1-acid glycoprotein (AAG)and correlative studies	X <sup>10</sup>	X <sup>1</sup> 0	X <sup>10</sup>	
Pregnancy test	X <sup>4</sup>			
Tissue block collection	X			
Toxicity Graded according to CTC V2.0	X	X	X <sup>7</sup>	X <sup>7</sup>

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 coumadin while on protocol therapy. To be done twice a week, weekly for 3 weeks; then weekly or more often as clinically indicated.

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**Revisions and Amendments**

<b>Type [Date]</b>	<b>Changes Made</b>	<b>Rationale</b>
Revision 1 [01 SEP 2001]	Minor wording changes and addition of the events vaginal bleeding, breakdown of womb lining, and drug fever to the risk section of the sample informed consent. Listed the regulatory authorities with access to patient data.	To update confidentiality and safety information to be provided to patients.
Revision 2 [08 NOV 2001]	NCIC CTG contacts updated for SAE reports and pharmacist contact at Kingston General Hospital, change in handling of plasma samples, and addition of Correlative Studies Manual. Corrected patient identification numbering scheme. Added information to be provided to IVRS at randomization. Prohibited prophylactic use of colony stimulating factors.	Administrative changes.  To prevent their use in place of a dose reduction.
Amendment 1 [20 FEB 2002]	Informed of the possibility of drug interaction between erlotinib and Coumadin® (warfarin). Eligibility criterion added and increased INR testing mandated. Sample informed consents updated with risk of bleeding, drug interaction, and liver enzyme abnormalities. Deleted "for advanced or metastatic disease" from population definition. Prior chemotherapy could have been adjuvant or for metastatic disease. Allowed patients with brain metastasis as the only site of PD to remain on-study if in their interest; the date of PD was the date of the new lesion. Clarified SAE reporting process for international centers. Responsibility for notifying international Investigators was changed from NCIC CTG to OSI. Specimen handling and shipping information reduced in the protocol due to provision of a separate lab manual.	To improve patient safety. Both drugs are highly protein bound and metabolized via the CYP3A4 pathway. To clarify the intended population and improve access to the study. To allow such patients to benefit from systemic disease control.  To expedite SAE reporting and to clarify OSI and NCIC CTG responsibilities. Administrative changes.
Amendment 2 [29 AUG 2002]	The sample size was changed from 330 to 700 in order to have 90% power to detect a 33% improvement in survival. The sample size was updated in the informed consents.	To detect a smaller but clinically relevant improvement in survival.
Amendment 3 [14 NOV 2002]	Management and dose adjustment recommendations were added for interstitial pneumonitis. Side effects of erlotinib were updated in the sample informed consents.	To update safety information.

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this page is the manifestation of the electronic signature.**

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/s/

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Martin Cohen  
10/8/04 09:48:16 AM  
MEDICAL OFFICER

John Johnson  
10/8/04 10:51:07 AM  
MEDICAL OFFICER  
See my Clinical Team Leader Review

**Clinical Team Leader Review  
Of NDA**

NDA            21743

DRUG           Tarceva (Erlotinib Hydrochloride)

APPLICANT    OSI Pharmaceuticals, Inc.

RECEIPT DATE   July 30, 2004

INDICATION    Patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen

**CLINICAL EVALUATION**

**Study Description**

The application is supported by a randomized controlled multicenter International study in patients with Stage IIIB or IV non-small cell lung cancer who had failed one or two prior chemotherapy regimens for locally advanced or metastatic disease. A total of 731 patients were randomized in a 2:1 ratio between Tarceva 150 mg orally daily or Placebo. 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). Treatment continued until disease progression or unacceptable toxicity. Crossover was not permitted.

**Efficacy Endpoints**

The primary endpoint was overall survival. Secondary endpoints were tumor response, tumor response duration, progression-free survival, quality of life (assessed by patient reported symptoms on the EORTC QLQ-C30 and QLQ LC-13 questionnaires) and to correlate the expression of epidermal growth factor receptor levels at diagnosis with outcomes and response to treatment.

## Patient Baseline Characteristics

The following Summaries of Baseline Patient Characteristics are copied from the Applicant's Tables 11-1, 11-5 and 11-6. Treatment groups are well balanced.

### Summary of Patient Baseline Characteristics

Characteristics	Erlotinib (N=488)		Placebo (N=243)	
	n	(%)	n	(%)
Gender				
Female	173	(35)	83	(34)
Male	315	(65)	160	(66)
Age (Years)				
18-39	6	(1)	5	(2)
40-64	293	(60)	148	(61)
65	189	(39)	90	(37)
Race				
White	379	(78)	188	(77)
Black	18	(4)	12	(5)
Native/Aboriginal	1	(<1)	0	(0)
Oriental	63	(13)	28	(12)
Indian Subcontinent	1	(<1)	0	(0)
Other	26	(5)	15	(6)
ECOG Performance Status				
0	64	(13)	34	(14)
1	256	(52)	132	(54)
2	126	(26)	56	(23)
3	42	(9)	21	(9)
Weight Loss in Previous 6 Months				
< 5%	320	(66)	166	(68)
5 - 10%	96	(20)	36	(15)
> 10%	52	(11)	29	(12)
Unknown	20	(4)	12	(5)
Smoking History				
Never smoked	104	(21)	42	(17)
Current or Ex-smoker	358	(73)	187	(77)
Unknown	26	(5)	14	(6)
Pack Years Smoked				
Number of pack-years < 20	36	(7)	12	(5)
Number of pack-years 20	291	(60)	166	(68)
Number of pack-years unknown <sup>a</sup>	57	(12)	23	(9)
NA, never smoked	104	(21)	42	(17)
Smoking at Study Entry				
Smoked within 1 year of study entry	56	(11)	29	(12)
Smoked beyond 1 year of study entry	166	(34)	77	(32)
Unknown <sup>a</sup>	162	(33)	95	(39)
NA, never smoked	104	(21)	42	(17)

### Summary of Previous Therapy for NSCLC

	n	Erlotinib (N=488)		n	Placebo (N=243)	
			(%)			(%)
Previous Therapy						
Chemotherapy	488		(100)	243		(100)
Surgery	487		(100)	242		(100)
Radiation	264		(54)	143		(59)
Hormonal Therapy	1		(<1)	1		(<1)
Other Prior Therapy	2		(<1)	2		(<1)
Number of Prior Chemotherapy Regimens						
1	243		(50)	121		(50)
2	238		(49)	119		(49)
3	7		(1)	3		(1)
Prior Platinum Therapy						
No	34		(7)	19		(8)
Yes	454		(93)	224		(92)
Prior Taxane Therapy						
No	311		(64)	153		(63)
Yes	177		(36)	90		(37)

APPEARS THIS WAY  
ON ORIGINAL

## Summary of Disease Characteristics

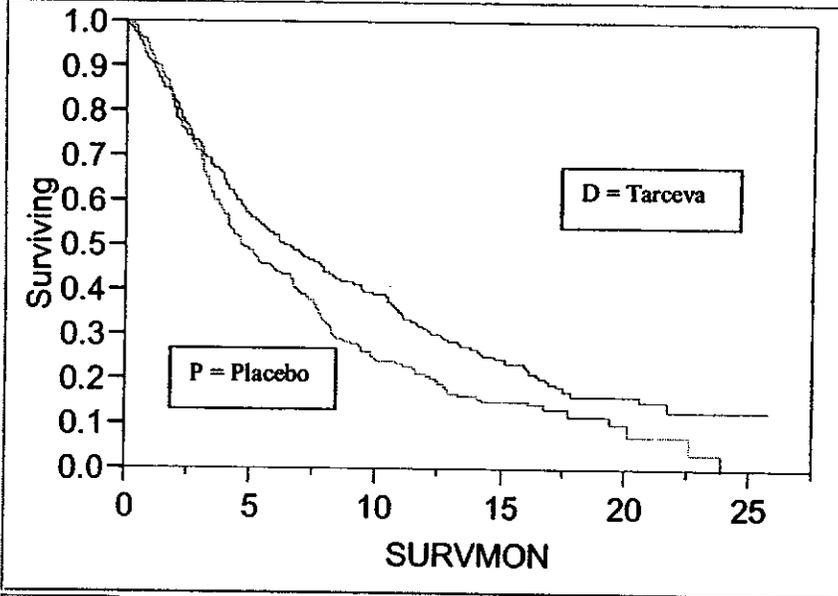
	Erlotinib (N=488)		Placebo (N=243)	
	N	(%)	N	(%)
<b>Histological Classification</b>				
Adenocarcinoma	246	(50)	119	(49)
Squamous	144	(30)	78	(32)
Undifferentiated Large Cell	41	(8)	23	(9)
Mixed Non-Small Cell	11	(2)	2	(<1)
Other	46	(9)	21	(9)
<b>Stage of Disease at First Diagnosis</b>				
IA	8	(2)	3	(1)
IB	15	(3)	8	(3)
IIA	5	(1)	5	(2)
IIB	11	(2)	11	(5)
IIIA	41	(8)	22	(9)
IIIB	182	(37)	91	(37)
IV	226	(46)	103	(42)
<b>Time From Initial Diagnosis to the Most Recent Progression/Relapse (Months)</b>				
<6	78	(16)	47	(19)
6 - 12	161	(33)	79	(33)
>12	246	(50)	114	(47)
Missing	3	(<1)	3	(1)
<b>Time From Initial Diagnosis to Randomization (Months)</b>				
<6	63	(13)	34	(14)
6 - 12	157	(32)	85	(35)
>12	268	(55)	124	(51)
<b>Time From the Most Recent Progression/Relapse to Randomization (Months)</b>				
<6	472	(97)	230	(95)
6 - 12	11	(2)	9	(4)
>12	3	(<1)	1	(<1)
Missing	2	(<1)	3	(1)

### Survival Results ITT

The following figure shows Kaplan Meier survival curves for a univariate analysis of treatment effect on survival.

## Overall Survival By Treatment N=731

### Product-Limit Survival Fit Survival Plot



Time to event:

SURVMON

Censored by

Surv Cens

Grouped by

TRTGROUP

#### Summary

Group	N Failed	N Censored	Mean	Std Dev
D	378	110	9.02692 Biased	0.34036
P	209	34	7.48694	0.44814
Combined	587	144	8.70082 Biased	0.29168

#### Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	6.6694	5.5195	7.7864	2.6612	14.
P	4.6982	4.1068	6.2752	2.4641	9.8
Combined	5.9795	5.1253	6.8008	2.6283	12.

#### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	9.7755	1	0.0018
Wilcoxon	6.0001	1	0.0143

#### Risk Ratios

Term	Risk Ratio	Lower CL	Upper CL
Rx	0.764033	0.644878	0.905204

### **Survival Results in Subgroups**

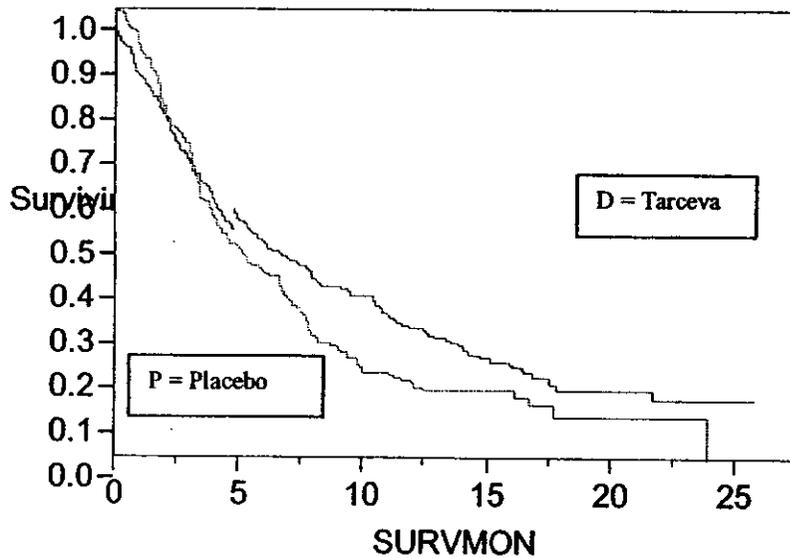
The following Figures show Kaplan Meier survival curves from univariate analyses of the treatment effect on survival in subgroups. Tarceva prolongs survival in both males and females, age < 60 and  $\geq$  60, squamous cell and adenocarcinoma, ECOG performance status 0 or 1 and 2 or 3, and 1 or > 1 prior chemotherapy regimens. Tarceva prolongs survival in patients with < Stage IV at initial diagnosis, but not in patients with Stage IV at initial diagnosis.

Tarceva prolongs survival in never smokers (HR=0.442, p=0.001), but there is no statistically significant effect in smokers (HR=0.865, p=0.141) and smokers stopped > 1 year (HR=0.815, p=0.143).

In the never smokers EGFR positive subgroup Tarceva prolongs survival (HR=0.279, p=0.003). But in the never smokers EGFR negative subgroup Tarceva has no apparent survival effect (HR=1.42, p=0.579).

*Appears This Way  
On Original*

**OS Males By Treatment N=475**



Time to event:  
SURVMON  
Censored by  
Surv Cens  
Grouped by  
TRTGROUP

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	249	66	8.60547 Biased	0.41983
P	139	21	7.12115	0.56263
Combined	388	87	8.29752 Biased	0.35961

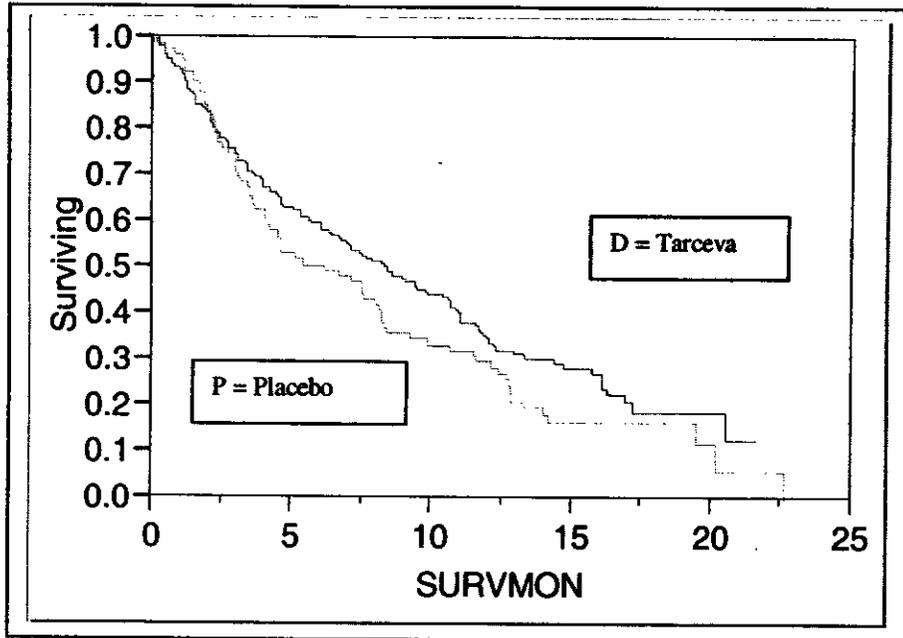
**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
D	5.7166	4.8296	6.9979	2.5626	14.
P	4.5339	3.6468	5.7823	2.2669	9.0
Combined	5.2238	4.6324	6.078	2.4641	12.

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.7632	1	0.0093
Wilcoxon	4.2074	1	0.0402

OS Females By Treatment N=256



Time to event:  
SURVMON  
Censored by  
Surv Cens  
Grouped by  
TRTGROUP

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	129	44	9.62761 Biased	0.55215
P	70	13	8.34325	0.76615
Combined	199	57	9.35184	0.47314

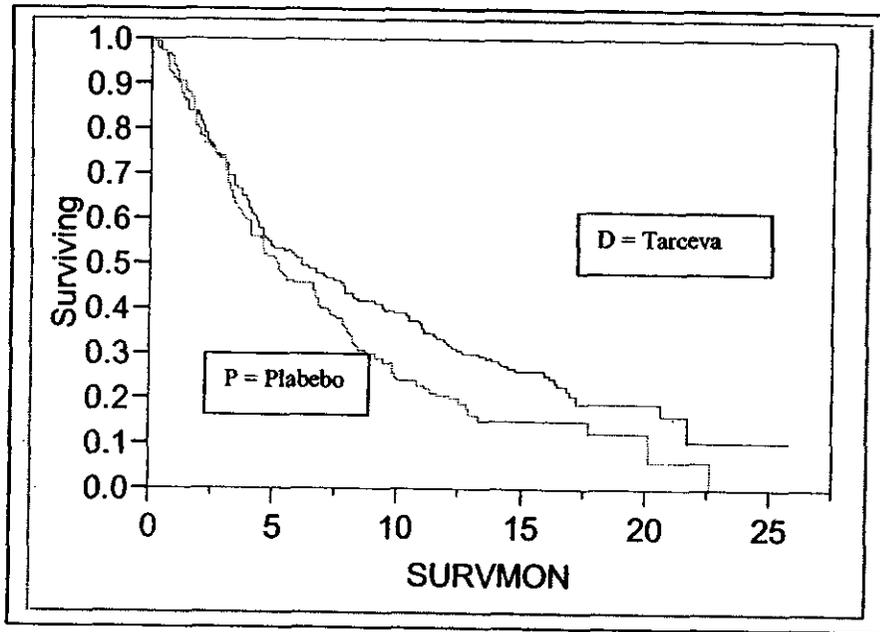
**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	8.4435	6.3737	10.71	3.0554	16.
P	6.1766	4.1068	8.2464	2.7269	12.
Combined	7.5893	6.1109	8.9692	2.9897	14.

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.3217	1	0.1276
Wilcoxon	1.4748	1	0.2246

OS Age < 60 By Treatment N=356



D —  
P - -

Time to event:  
SURVMON  
Censored by  
Sur Cen  
Grouped by  
TRTGROUP

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	171	54	9.18929 Biased	0.51718
P	111	20	7.56934	0.5969
Combined	282	74	8.6703 Biased	0.40441

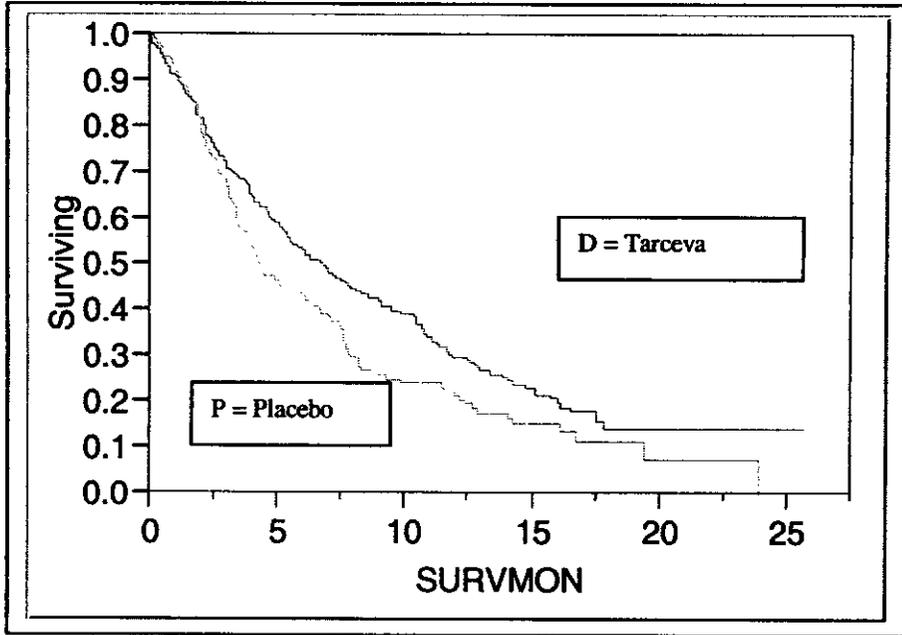
**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	6.1109	4.6653	7.9179	2.6612	16.
P	5.191	4.1068	6.8337	2.6283	9.9
Combined	5.7823	4.6653	6.9979	2.6612	13.

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.6200	1	0.0316
Wilcoxon	2.0855	1	0.1487

OS Age ≥ 60 By Treatment N=375



Time to event:  
SURVMON  
Censored by  
Sur Cen  
Grouped by  
TRTGROUP

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	207	56	8.32833 Biased	0.3834
P	98	14	7.35256	0.66849
Combined	305	70	8.64536 Biased	0.40371

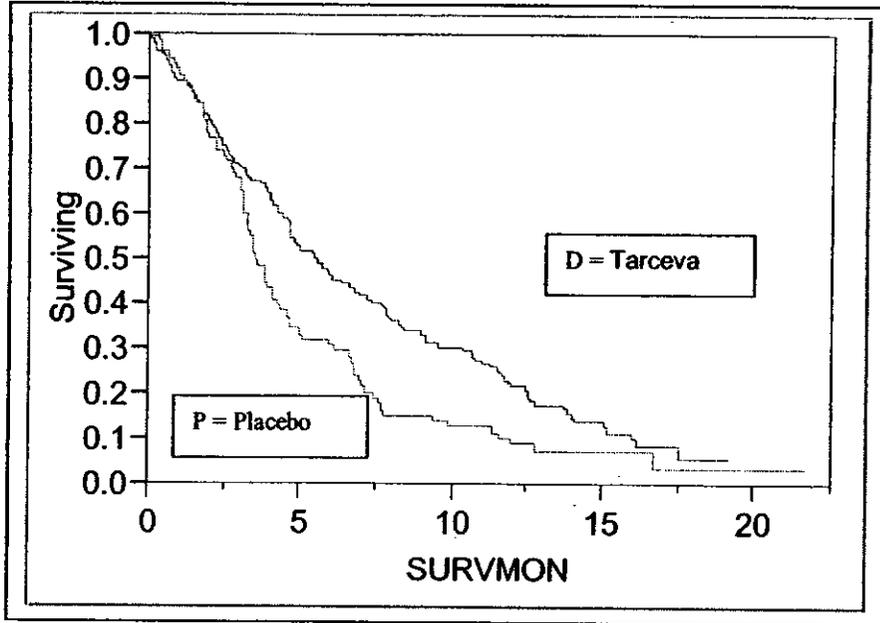
**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	6.8008	5.4209	8.0821	2.5955	14.
P	4.3368	3.5154	6.2752	2.3655	9.2
Combined	6.1109	5.0924	7.1951	2.5298	12.

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.8735	1	0.0273
Wilcoxon	3.9561	1	0.0467

OS Squamous By Treatment N=222



D —  
P —

Time to event:  
SURVMON  
Censored by  
Surv Cens  
Grouped by  
TRTGROUP

Summary

Group	N Failed	N Censored	Mean	Std Dev
D	126	18	7.16836 Biased	0.45456
P	73	5	5.19146 Biased	0.49275
Combined	199	23	6.48541 Biased	0.34879

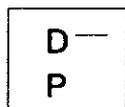
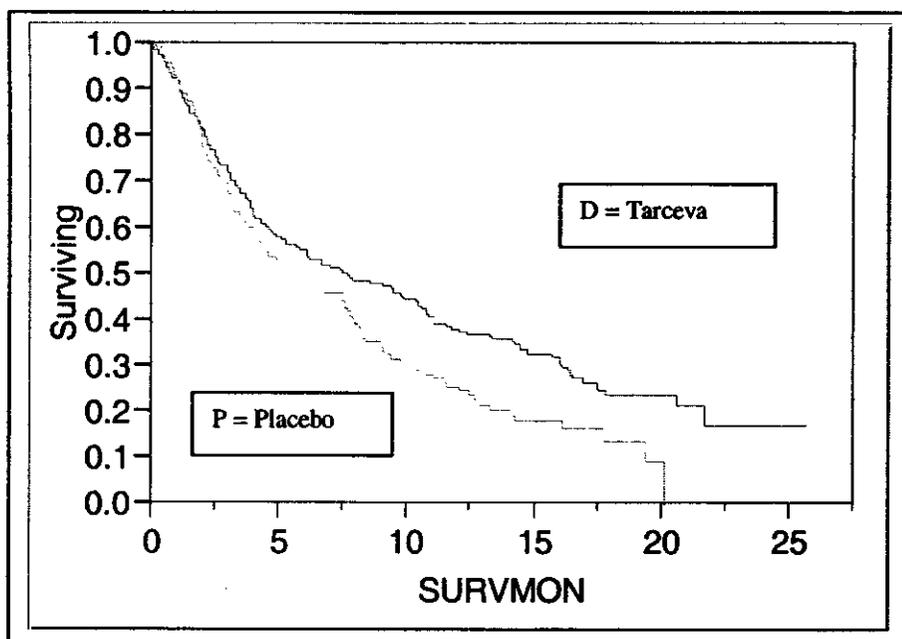
Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
D	5.6181	4.5996	6.9979	2.5298	11.
P	3.5154	3.1211	4.3368	2.2669	6.8
Combined	4.6653	4.0411	5.6181	2.4312	9.5

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	7.1857	1	0.0073
Wilcoxon	6.2942	1	0.0121

### OS Adenocarcinoma By Treatment N=365



Time to event:  
SURVMON  
Censored by  
Surv Cens  
Grouped by  
TRTGROUP

#### Summary

Group	N Failed	N Censored	Mean	Std Dev
D	173	73	10.0731 Biased	0.52371
P	99	20	7.82773	0.60347
Combined	272	93	9.36284 Biased	0.41041

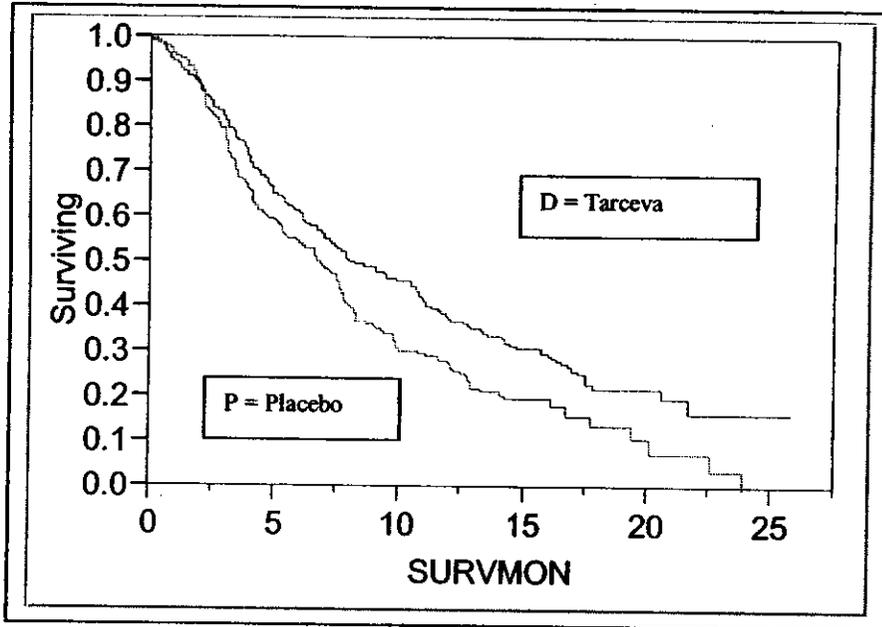
#### Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	7.7536	5.4209	10.48	2.6612	11
P	5.3552	4.1068	7.7864	2.2669	12
Combined	6.9979	5.2895	8.1807	2.5298	16

#### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	7.0927	1	0.0077
Wilcoxon	3.4192	1	0.0644

OS ECOG 0 or 1 By Treatment N=486



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
TRTGROUP

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	229	91	10.4748 Biased	0.43009
P	137	29	8.65715	0.55352
Combined	366	120	10.0881 Biased	0.36925

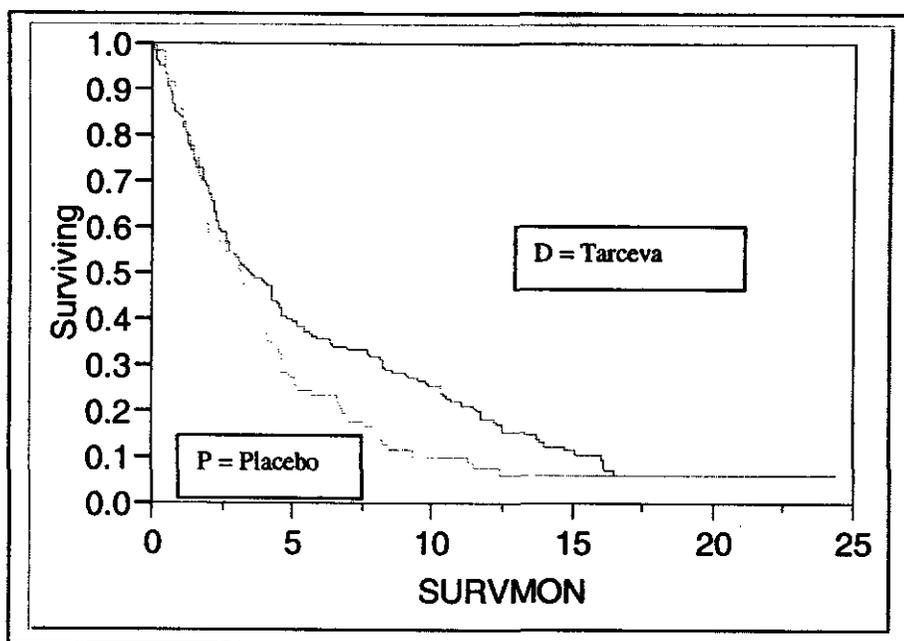
**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
D	8.2464	6.9979	10.612	3.9097	17.
P	6.8008	5.191	7.7864	3.154	12.
Combined	7.6879	6.8008	8.345	3.5154	16.

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	8.7972	1	0.0030
Wilcoxon	5.4393	1	0.0197

OS ECOG 2 or 3 By Treatment N=245



D —  
P - -

Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
TRTGROUP

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	149	19	5.92821 Biased	0.41965
P	72	5	4.16438 Biased	0.40181
Combined	221	24	5.45709 Biased	0.32778

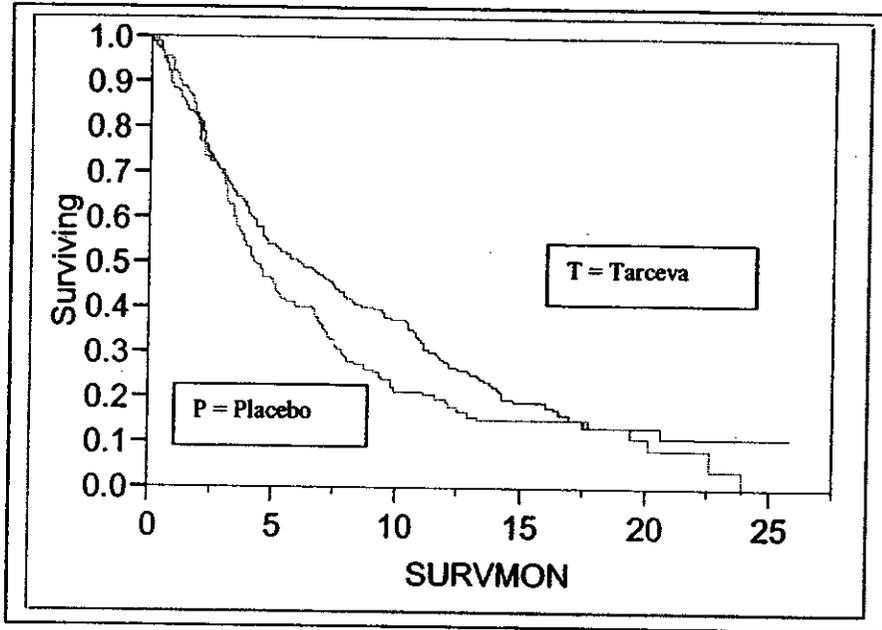
**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	3.5811	2.6612	4.5996	1.5113	10.
P	3.1869	1.9055	3.8439	1.6427	5.2
Combined	3.3183	2.694	4.1396	1.577	8.2

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.3574	1	0.0669
Wilcoxon	1.9644	1	0.1610

**OS 2 or More Prior Regimens By Treatment N=362**



D —  
P —

Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
TRTGROUP

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	193	48	8.30167 Biased	0.44646
P	107	14	7.23403	0.63335
Combined	300	62	8.20047 Biased	0.3997

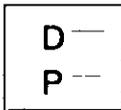
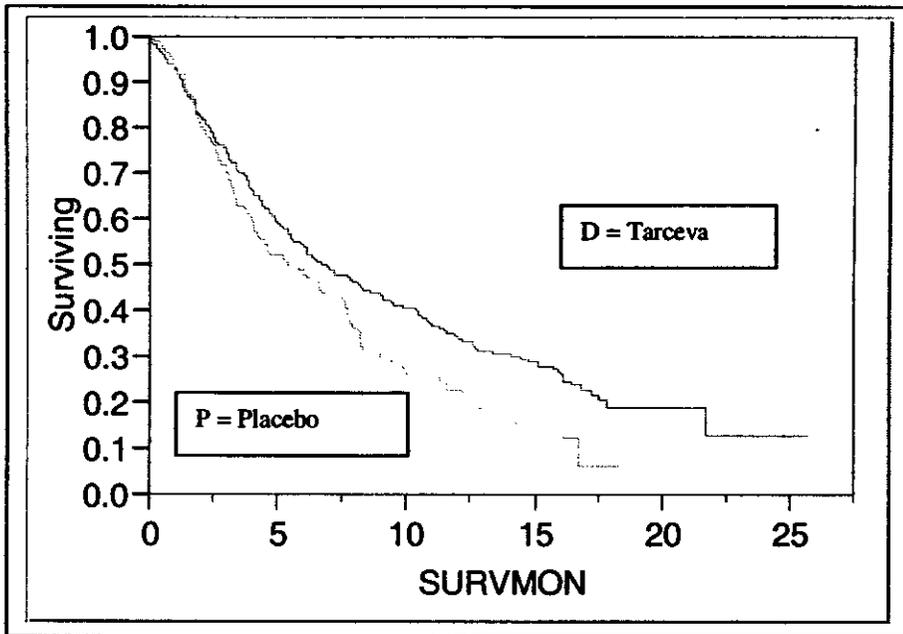
**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	6.078	4.6653	7.7536	2.3655	13.
P	4.3696	3.5483	5.5524	2.2669	9.2
Combined	5.2238	4.4682	6.768	2.2998	12.

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.6060	1	0.0576
Wilcoxon	2.5574	1	0.1098

OS 1 Prior Regimen By Treatment N=369



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
TRTGROUP  
**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	185	62	9.60094 Biased	0.49357
P	102	20	7.15574 Biased	0.49065
Combined	287	82	8.95516 Biased	0.38826

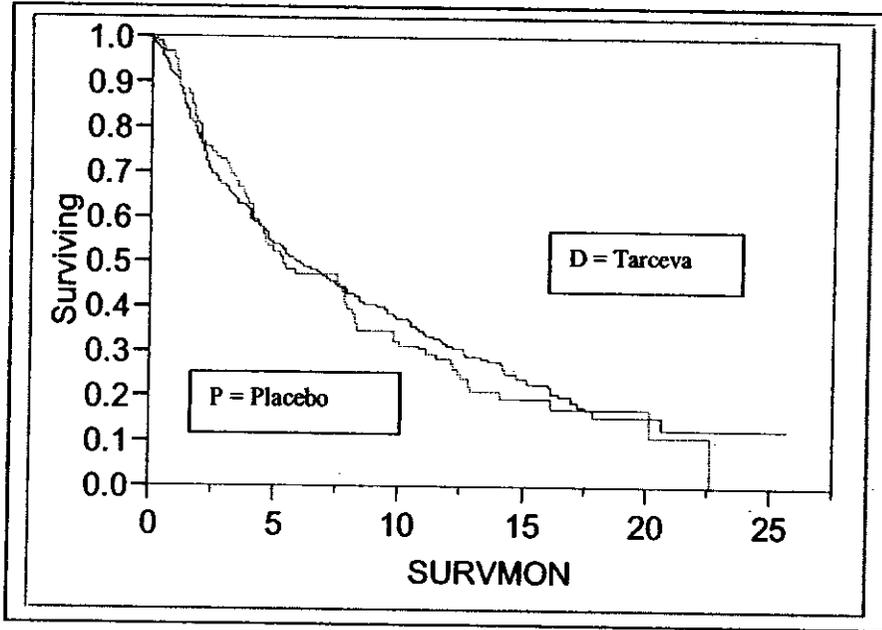
**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	6.8994	5.5195	8.9692	3.0226	16.
P	5.4538	4.1068	7.6222	2.6283	11.
Combined	6.4723	5.4209	7.7207	2.8583	14.

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.5036	1	0.0108
Wilcoxon	3.5018	1	0.0613

OS Stage IV at Initial Diagnosis By Treatment N=329

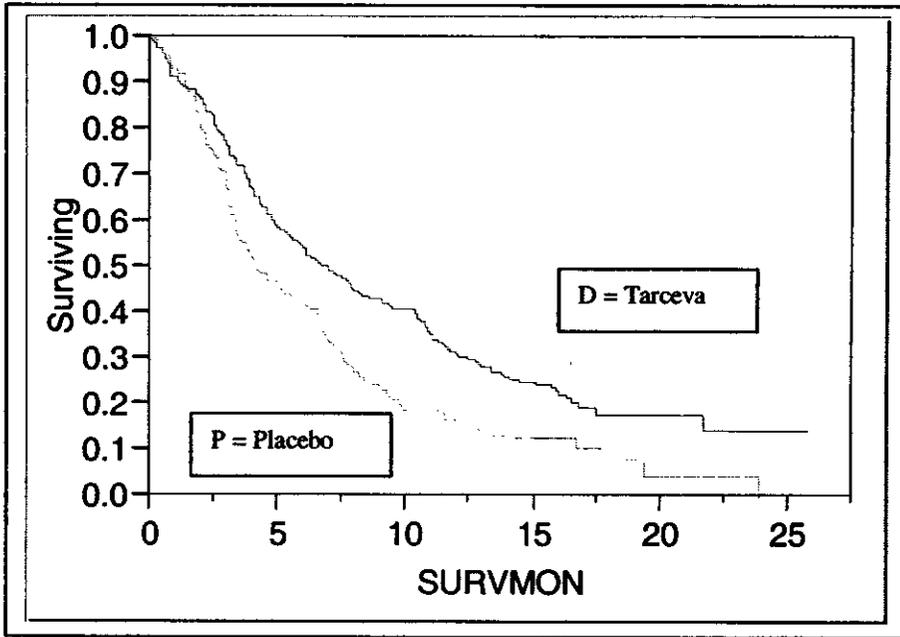


D —  
P —

Time to event:  
SURVMON  
Censored by  
Sur Cen  
Grouped by  
TRTGROUP  
**Summary**

Group	N Failed	N Censored	Mean	Std Dev	
D	177	49	8.5811 Biased	0.46377	
P	83	20	8.45688	0.74387	
Combined	260	69	8.70639 Biased	0.42581	
<b>Quantiles</b>					
Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	5.9795	4.6982	7.885	2.1684	14.
P	5.3552	4.1725	7.8193	2.3984	12.
Combined	5.7495	4.6982	7.6879	2.2012	14.
<b>Tests Between Groups</b>					
Test	ChiSquare	DF	Prob>ChiSq		
Log-Rank	0.3550	1	0.5513		
Wilcoxon	0.0162	1	0.8988		

**OS < Stage IV at Initial Diagnosis By Treatment N=402**



D	—
P	- - -

Time to event:  
SURVMON  
Censored by  
Sur Cen  
Grouped by  
TRTGROUP  
**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	201	61	9.29009 Biased	0.46336
P	126	14	6.72935	0.53415
Combined	327	75	8.59019 Biased	0.38684

**Quantiles**

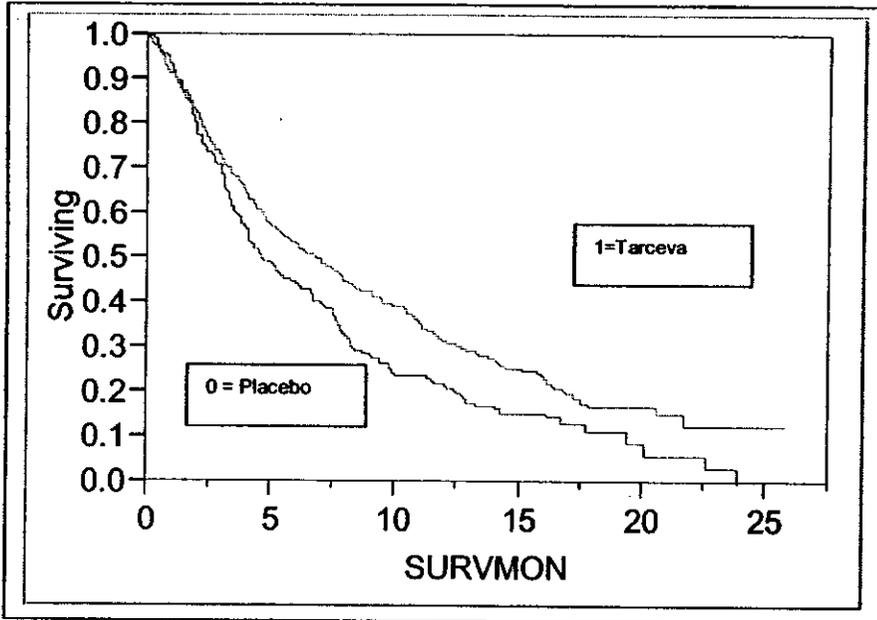
Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	6.9979	5.6181	8.2464	3.154	14.
P	4.271	3.4497	6.1788	2.5298	8.7
Combined	6.078	4.961	6.8008	2.9897	12.

**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	14.2071	1	0.0002
Wilcoxon	11.3893	1	0.0007

OS Known Smoking Status By Rx N = 691

Product-Limit Survival Fit  
Survival Plot



0 ---  
1 ---

Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
rx

Summary

Group	N Failed	N Censored	Mean	Std Dev
0	197	32	7.38129	0.45454
1	356	106	9.10834 Biased	0.35043
Combined	553	138	8.72028 Biased	0.29989

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
0	4.6653	4.0082	6.1766	2.3655	9.8
1	6.8008	5.5195	7.885	2.7269	15.
Combined	6.078	5.191	6.9979	2.5955	13.

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	10.8044	1	0.0010
Wilcoxon	7.0584	1	0.0079

Risk Ratios

Term	Risk Ratio	Lower CL	Upper CL
rx	0.775074	0.660796	0.909114

**OS Known Smoking Status By Rx and Smoking Status N = 691**

**Proportional Hazards Fit**

Censored By: Surv Cen

**Whole Model**

Number of Events		553			
Number of Censorings		138			
Total Number		691			
Model	-LogLikelihood		ChiSquare	DF	Prob>ChiSq
Difference	12.880		25.7599	2	<.0001
Full	3224.174				
Reduced	3237.054				

**Parameter Estimates**

Term	Estimate	Std Error	Lower CL	Upper CL
rx	-0.2549754	0.0894816	-0.430356	-0.078068
smoke_0	-0.4173747	0.1108824	-0.639788	-0.204666

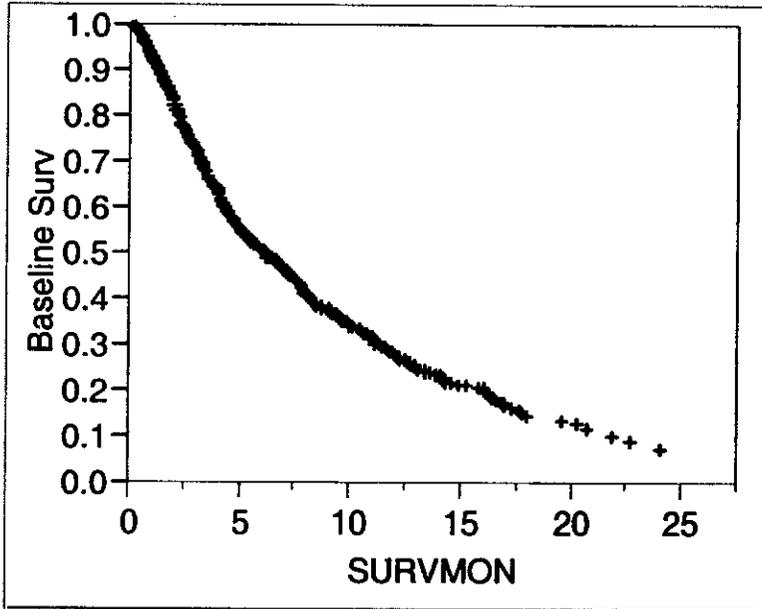
**Risk Ratios**

Term	Risk Ratio	Lower CL	Upper CL
rx	0.774936	0.650277	0.924902
smoke_0	0.658774	0.527404	0.814919

**Effect Likelihood Ratio Tests**

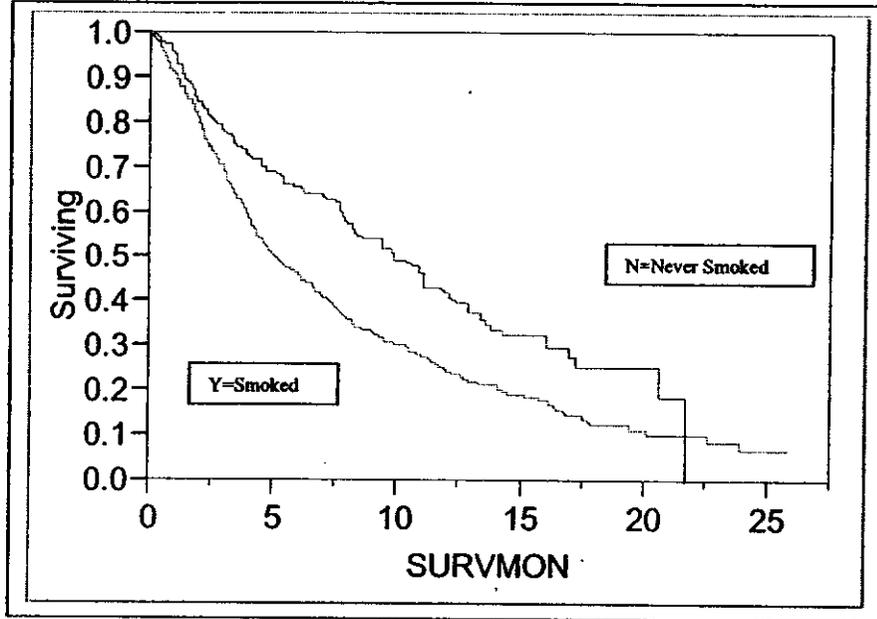
Source	Nparm	DF	L-R ChiSquare	Prob>ChiSq
rx	1	1	7.91393002	0.0049
smoke_0	1	1	15.3898655	0.0001

**Baseline Survival at mean**



### OS By Smoking Status N = 691

#### Product-Limit Survival Fit Survival Plot



N —  
Y —

Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
SMHAS

#### Summary

Group	N Failed	N Censored	Mean	Std Dev
N	101	45	10.955	0.65041
Y	452	93	8.0643 Biased	0.32413
Combined	553	138	8.72028 Biased	0.29989

#### Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
N	9.8891	7.9507	11.926	3.5483	20.
Y	5.0924	4.4682	6.0452	2.4312	11.
Combined	6.078	5.191	6.9979	2.5955	13.

#### Tests Between Groups

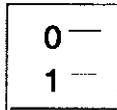
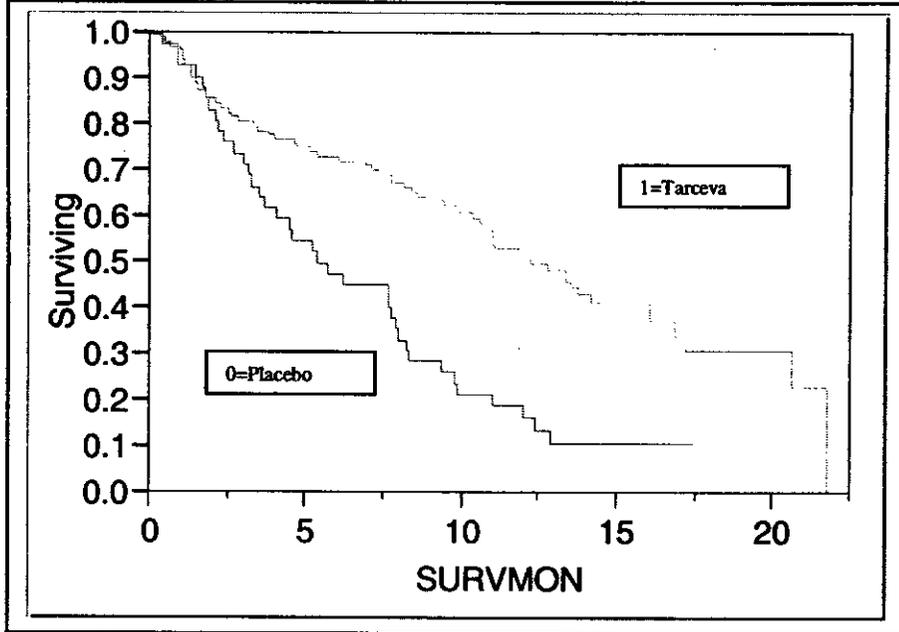
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	16.6455	1	<.0001
Wilcoxon	16.8767	1	<.0001

#### Risk Ratios

Term	Risk Ratio	Lower CL	Upper CL
smoke_0	0.640216	0.513001	0.791193

OS Never Smoked By Rx N=146

Product-Limit Survival Fit  
Survival Plot



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
Rx

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
0	37	5	6.42339 Biased	0.64066
1	64	40	12.4176	0.76692
Combined	101	45	10.955	0.65041

**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
0	5.4538	3.5483	7.9507	2.694	9.8
1	12.255	10.382	16.131	5.1581	20.
Combined	9.8891	7.9507	11.926	3.5483	20.

**Tests Between Groups**

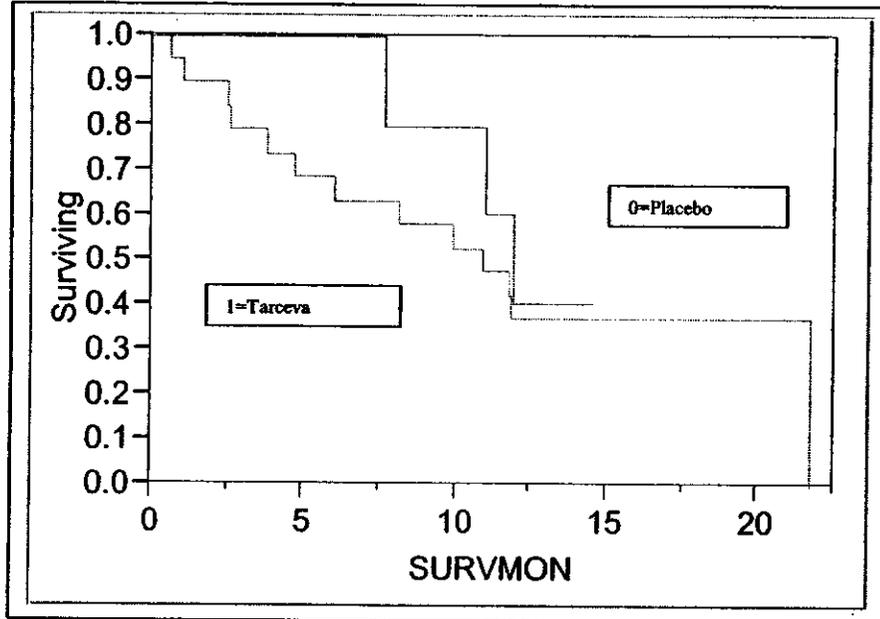
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	17.4768	1	<.0001
Wilcoxon	14.0411	1	0.0002

**Risk Ratios**

Term	Risk Ratio	Lower CL	Upper CL
Rx	0.42229	0.279886	0.645568

OS Never Smoked EGFR Negative By Rx N = 24

Product-Limit Survival Fit  
Survival Plot



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
Rx

Summary

Group	N Failed	N Censored	Mean	Std Dev
0	3	2	10.9864 Biased	0.92723
1	13	6	11.9486	1.94951
Combined	16	8	12.5135	1.65036

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
0	12.057	7.6879	.	11.072	
1	10.94	3.9097	.	3.9097	21.
Combined	11.828	6.078	.	6.078	21.

Tests Between Groups

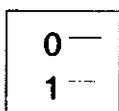
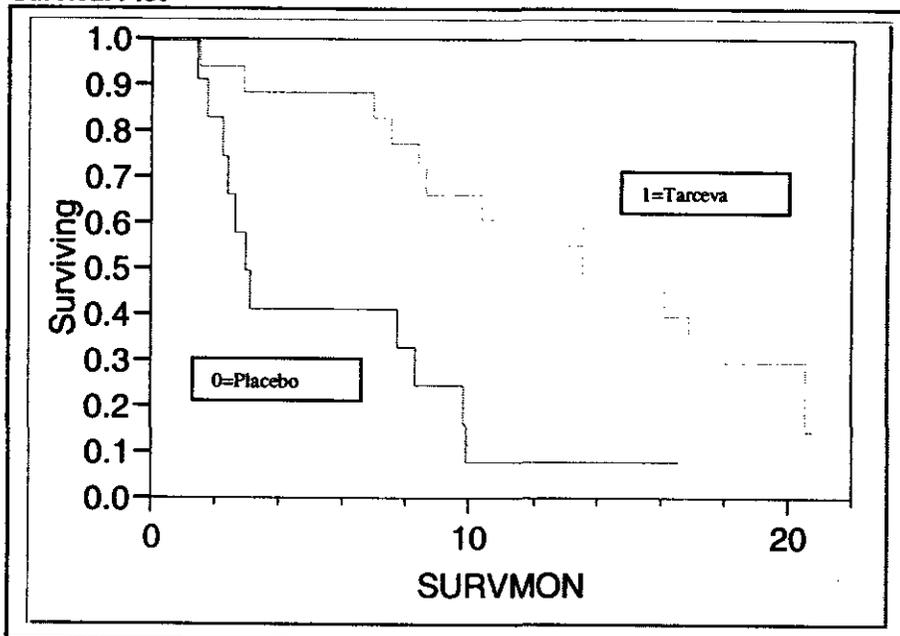
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.3072	1	0.5794
Wilcoxon	0.7888	1	0.3745

Risk Ratios

Term	Risk Ratio	Lower CL	Upper CL
Rx	1.428677	0.452258	6.282757

OS Never Smoked EGFR Positive By Rx N = 30

Product-Limit Survival Fit  
Survival Plot



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
Rx

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
0	11	1	5.21561 Biased	1.03172
1	12	6	13.3709 Biased	1.57612
Combined	23	7	10.4535 Biased	1.30231

**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
0	3.1869	1.7741	9.8563	2.3984	9.8
1	13.602	8.4435	20.632	8.4435	20.
Combined	9.8563	6.9979	13.602	3.0226	16.

**Tests Between Groups**

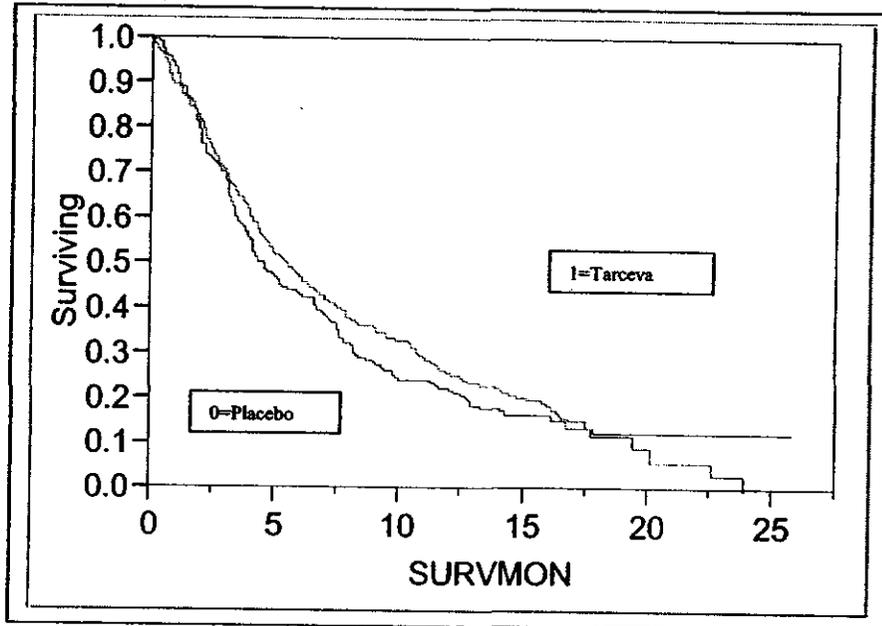
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	9.1296	1	0.0025
Wilcoxon	9.4439	1	0.0021

**Risk Ratios**

Term	Risk Ratio	Lower CL	Upper CL
Rx	0.2729	0.109694	0.669523

## OS Smokers By Rx N = 545

### Product-Limit Survival Fit Survival Plot



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
Rx

#### Summary

Group	N Failed	N Censored	Mean	Std Dev
0	160	27	7.40059	0.51146
1	292	66	7.65514 Biased	0.32171
Combined	452	93	8.0643 Biased	0.32413

#### Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
0	4.6324	3.8439	6.1766	2.2669	9.9
1	5.5195	4.6653	6.5051	2.5298	12.
Combined	5.0924	4.4682	6.0452	2.4312	11.

#### Tests Between Groups

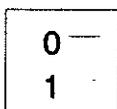
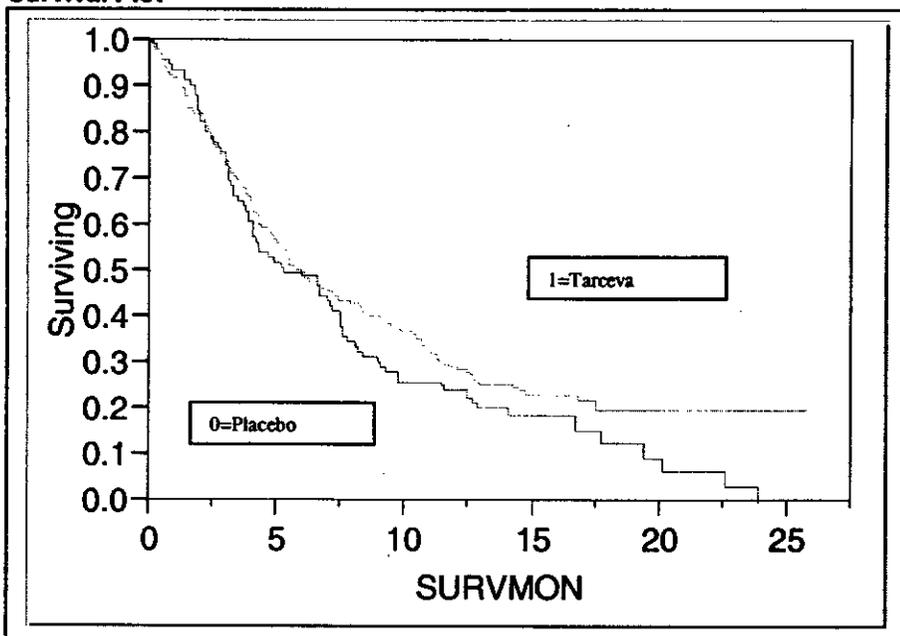
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.1672	1	0.1410
Wilcoxon	1.3273	1	0.2493

#### Risk Ratios

Term	Risk Ratio	Lower CL	Upper CL
Rx	0.8654	0.714656	1.051731

## OS Stopped Smoking > 1 Year By Rx N = 278

### Product-Limit Survival Fit Survival Plot



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
Rx

#### Summary

Group	N Failed	N Censored	Mean	Std Dev
0	80	12	7.96644	0.72387
1	143	43	8.21815 Biased	0.45397
Combined	223	55	8.90176 Biased	0.47919

#### Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
0	5.9795	4.1068	7.4908	3.0226	11
1	6.0452	4.9281	7.9507	2.9897	14.
Combined	5.9795	4.9281	7.1951	3.0226	12.

#### Tests Between Groups

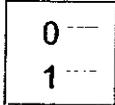
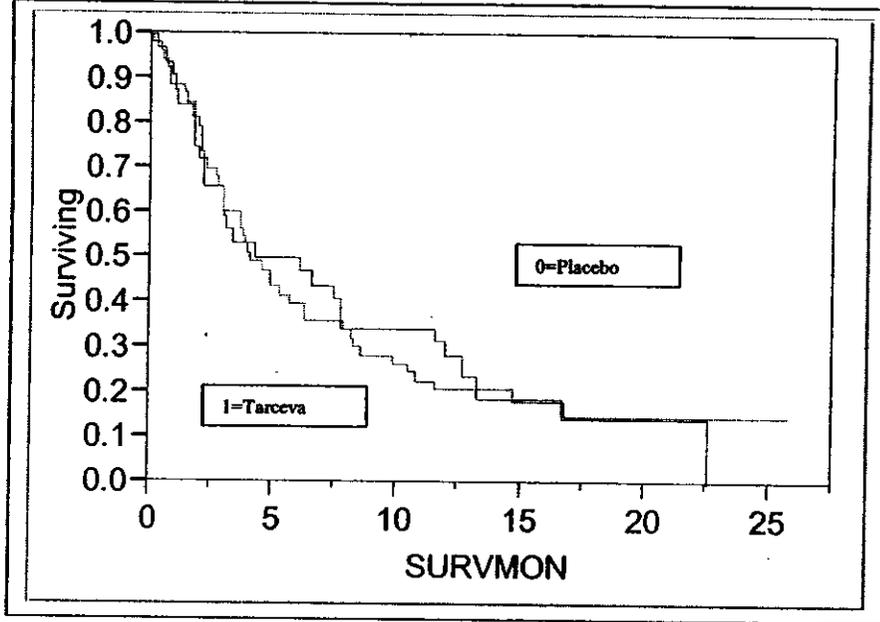
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.1428	1	0.1432
Wilcoxon	0.5907	1	0.4422

#### Risk Ratios

Term	Risk Ratio	Lower CL	Upper CL
Rx	0.815465	0.621874	1.076874

OS Smokers-EGFR Negative By Rx N = 85

Product-Limit Survival Fit  
Survival Plot



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
Rx

Summary

Group	N Failed	N Censored	Mean	Std Dev
0	27	5	8.09035	1.37379
1	44	9	6.76487 Biased	0.79691
Combined	71	14	7.79401 Biased	0.82158

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
0	6.1766	2.2341	11.63	2.0041	12.0041
1	4.1396	2.9897	6.3737	2.1684	10.1684
Combined	4.3368	3.0554	6.6037	2.1684	10.1684

Tests Between Groups

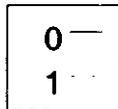
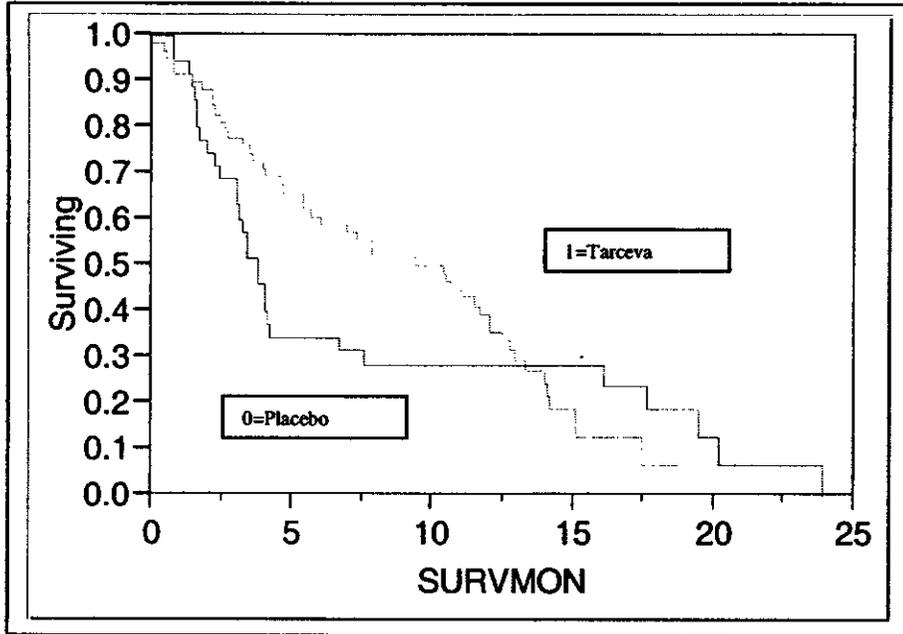
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.0086	1	0.9262
Wilcoxon	0.0284	1	0.8662

Risk Ratios

Term	Risk Ratio	Lower CL	Upper CL
Rx	1.022919	0.636996	1.673051

## OS Smokers-EGFR Positive By Rx N = 93

### Product-Limit Survival Fit Survival Plot



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
Rx

#### Summary

Group	N Failed	N Censored	Mean	Std Dev
0	30	5	7.78619	1.36051
1	46	12	8.96664 Biased	0.76471
Combined	76	17	8.77476	0.75691

#### Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
0	3.8439	3.1211	4.271	2.0041	16.
1	9.4949	5.5195	12.057	3.5811	14.
Combined	6.078	4.1068	10.513	2.7598	14.

#### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.3363	1	0.5620
Wilcoxon	3.1742	1	0.0748

#### Risk Ratios

Term	Risk Ratio	Lower CL	Upper CL
Rx	0.865268	0.53449	1.430381
Rx	1	1	0.33064838

0.5653

### **Survival Results By EGFR Status—Univariate Analyses**

EGFR expression status was determined by [redacted] using the DAKO EGFR pharmDx™ kit, without knowledge of treatment assignment. Scoring was performed according to the recommendations in the manufacturer's instructions. A positive EGFR expression was defined as having at least 10% of cells staining for EGFR.

Tarceva targets the EGF receptor. Thus there is great interest in whether Tarceva treatment effect is impacted by EGFR status. The following univariate analyses in the 238 (33%) patients with known EGFR status indicate that Tarceva clearly prolongs survival in EGFR positive patients (median Tarceva 10.7 mo vs Placebo 3.8 mo, HR= 0.646). In EGFR negative patients there is no apparent Tarceva effect on survival (median Tarceva 5.4 mo vs Placebo 7.5 mo, HR = 1.01). However, the 95% confidence intervals are wide and overlap for the EGFR positive and negative groups. Thus a favorable Tarceva survival effect in the EGFR negative subgroup can not be excluded with certainty.

EGFR status does not appear to be an important prognostic factor INDEPENDENT of treatment as shown by the similar survival of EGFR positive and negative patients on the Placebo treatment arm. In the Tarceva treatment group the superior survival of EGFR positive patients to EGFR negative patients indicates that EGFR status is a treatment DEPENDENT factor. The two univariate analyses of treatment effect in the EGFR positive and EGFR negative subgroups also indicate that EGFR status is a treatment DEPENDENT factor.

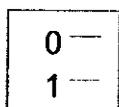
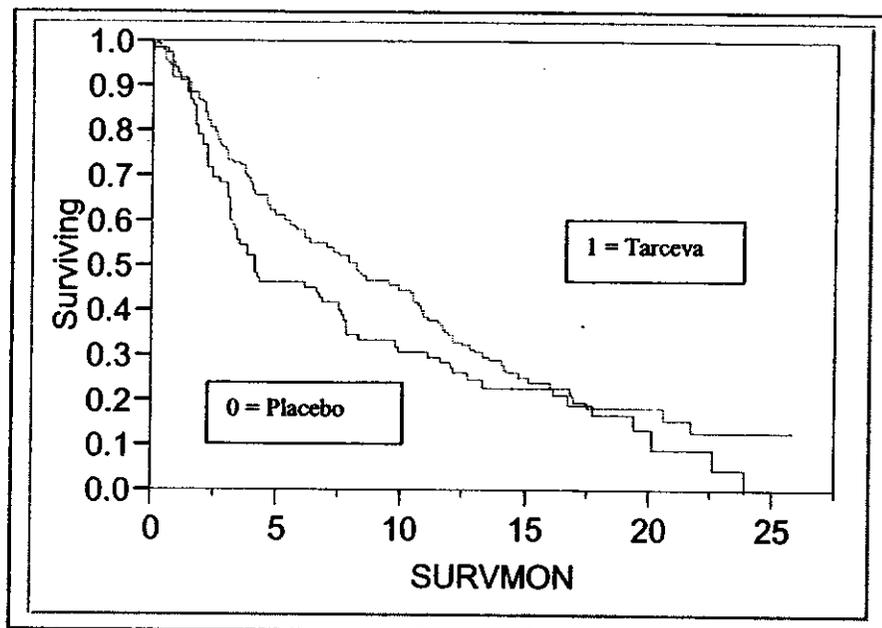
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**Treatment Effect on Survival by EGFR Status  
Applicant Table**

Pretreatment Characteristics	Erlotinib		Placebo		Hazard Ratio (95% CI)	Log-Rank p-value
	N	Median Survival Months (95% CI)	N	Median Survival Months (95% CI)		
EGFR Status						
Positive	78	10.71 (7.92, 12.85)	49	3.84 (3.12, 6.80)	0.65 (0.43, 0.97)	0.033
Negative	74	5.35 (3.91, 8.28)	37	7.49 (3.09, 12.02)	1.01 (0.65, 1.59)	0.958
Unknown	33 6	6.05 (4.86, 7.20)	157	5.09 (4.11, 6.60)	0.76 (0.61, 0.93)	0.008

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**OS EGFR Status Known By Treatment N = 238**



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
Rx

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
0	72	14	8.20812	0.83669
1	117	35	9.7003 Biased	0.60665
Combined	189	49	9.34371 Biased	0.51881

**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
0	4.1396	3.1869	7.6222	2.2669	12.
1	8.2464	5.7823	10.513	2.9897	15.
Combined	6.9979	4.8953	8.2793	2.694	14.

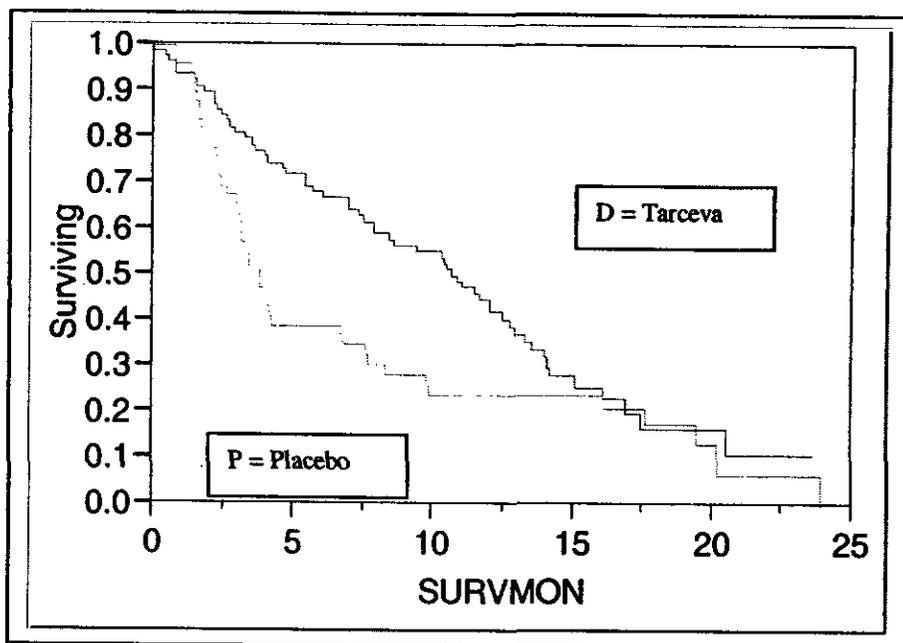
**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.0573	1	0.0804
Wilcoxon	3.8677	1	0.0492

**Risk Ratios**

Term	Risk Ratio	Lower CL	Upper CL
Rx	0.769922	0.575246	1.037532

OS EGFR Positive By Treatment N=127



D —  
P - -

Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
TRTGROUP

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	58	20	10.5519 Biased	0.77497
P	42	7	7.64292	1.1019
Combined	100	27	9.67762	0.69467

**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	10.71	7.5236	12.846	4.1396	16.
P	3.8439	3.1211	6.768	2.2669	9.8
Combined	7.7864	4.7639	10.48	3.0226	16.

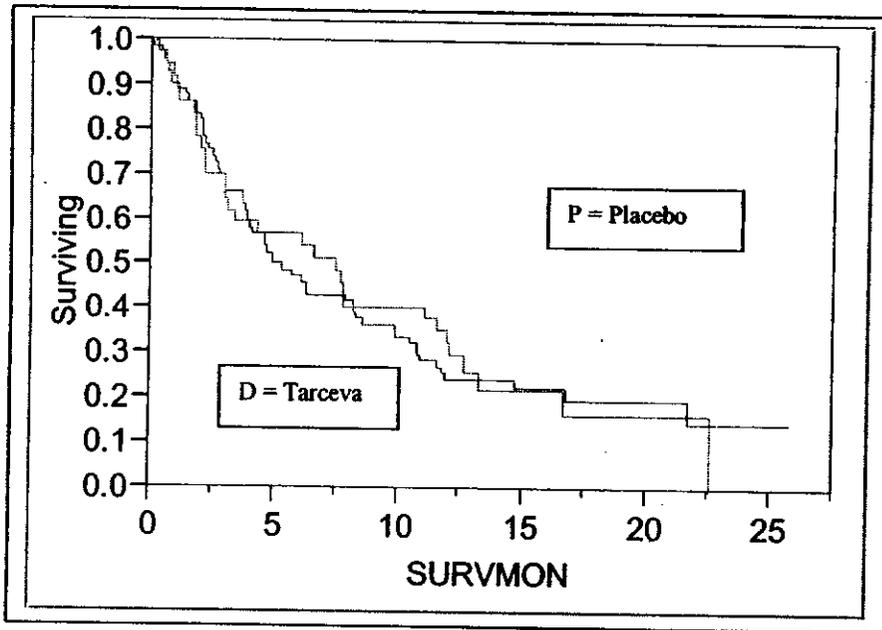
**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.5317	1	0.0333
Wilcoxon	8.8420	1	0.0029

**Risk Ratios**

Term	Risk Ratio	Lower CL	Upper CL
Rx	0.645842	0.431776	0.974835

**OS EGFR Negative By Treatment N=111**



D —  
P - -

Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
TRTGROUP

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	59	15	8.63533 Biased	0.89265
P	30	7	9.01327	1.30728
Combined	89	22	8.84051 Biased	0.74898

**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	5.3552	3.9097	8.2793	2.5626	11.
P	7.4908	3.0883	12.025	2.2341	13.
Combined	6.078	3.9425	8.1807	2.2669	12.

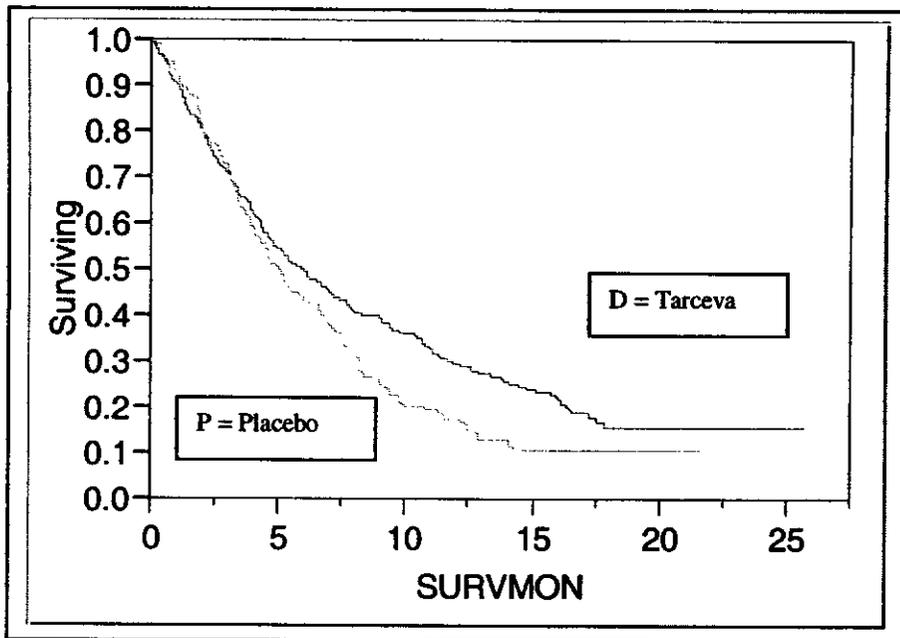
**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.0028	1	0.9581
Wilcoxon	0.0471	1	0.8281

**Risk Ratios**

Term	Risk Ratio	Lower CL	Upper CL
Rx	1.011876	0.656818	1.591861

**OS EGRF Unknown By Treatment N=493**



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
TRTGROUP

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
D	261	75	8.11753 Biased	0.34703
P	137	20	6.29417 Biased	0.35176
Combined	398	95	7.6584 Biased	0.27244

**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
D	6.0452	4.8624	7.1951	2.4641	14.
P	5.0924	4.1068	6.6037	2.7269	9.0
Combined	5.4538	4.8296	6.6694	2.5626	12.

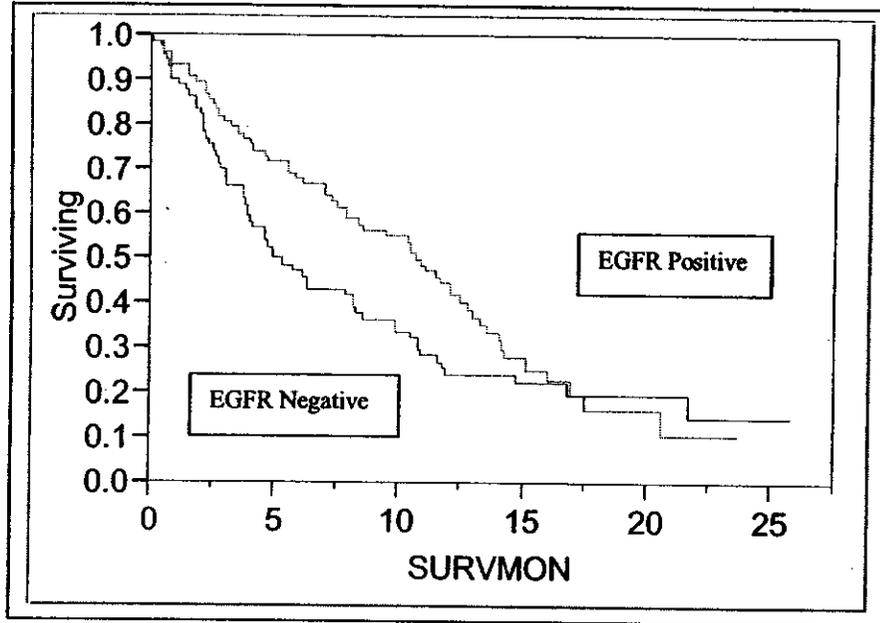
**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.9335	1	0.0085
Wilcoxon	2.5419	1	0.1109

**Risk Ratios**

Term	Risk Ratio	Lower CL	Upper CL
Rx	0.756703	0.615479	0.934353

**OS Tarceva By EGFR N=152**



Negative ---  
Positive ---

Time to event:

SURVMON

Censored by

Surv Cen

Grouped by

EGRESULT

**Summary**

Group	N Failed	N Censored	Mean	Std Dev
Negative	59	15	8.63533 Biased	0.89265
Positive	58	20	10.5519 Biased	0.77497
Combined	117	35	9.7003 Biased	0.60665

**Quantiles**

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
Negative	5.3552	3.9097	8.2793	2.5626	11.
Positive	10.71	7.5236	12.846	4.1396	16.
Combined	8.2464	5.7823	10.513	2.9897	15.

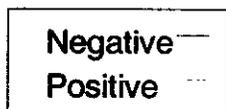
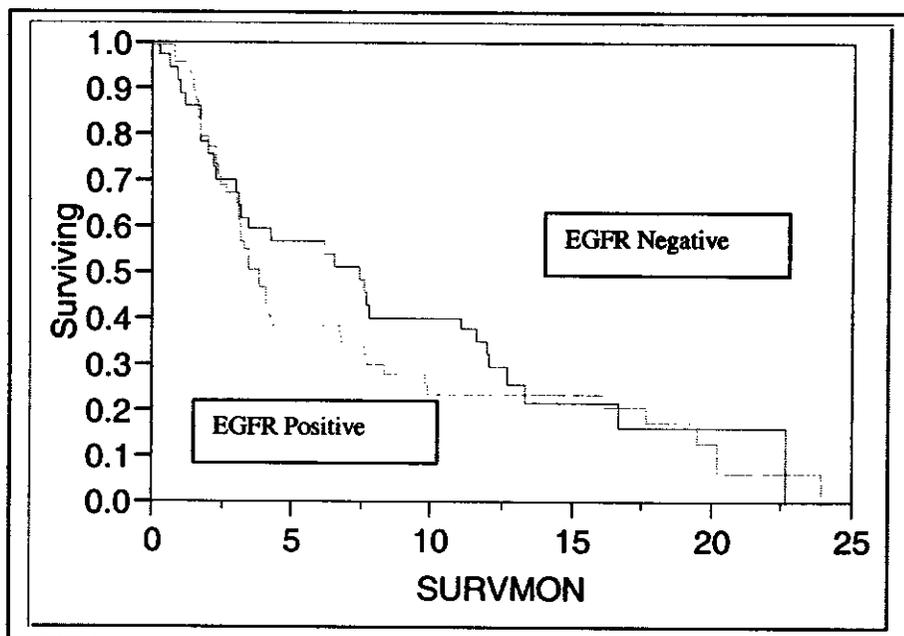
**Tests Between Groups**

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.5536	1	0.1100
Wilcoxon	5.9416	1	0.0148

**Risk Ratios**

Term	Risk Ratio	Lower CL	Upper CL
egfr-n	0.743761	0.515748	1.072322

### OS Placebo By EGFR N=86



Time to event:  
SURVMON  
Censored by  
Surv Cen  
Grouped by  
EGRESULT

#### Summary

Group	N Failed	N Censored	Mean	Std Dev
Negative	30	7	9.01327	1.30728
Positive	42	7	7.84292	1.1019
Combined	72	14	8.20812	0.83669

#### Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Fail
Negative	7.4908	3.0883	12.025	2.2341	13.
Positive	3.8439	3.1211	6.768	2.2669	9.8
Combined	4.1396	3.1869	7.6222	2.2669	12.

#### Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.3331	1	0.5638
Wilcoxon	0.4697	1	0.4931

#### Risk Ratios

Term	Risk Ratio	Lower CL	Upper CL
egrif_n	1.149477	0.717623	1.862029

### **Survival Results By EGFR Status—Multivariate Analyses**

Patients were not stratified by EGFR status prior to randomization, so there could be imbalances in important prognostic factors in the EGFR subgroups. The FDA statistician, Dr. Sridhara's analyses of this issue are presented below. There are imbalances of some prognostic factors in the subgroup of patients with known EGFR status, some favoring Tarceva and some favoring Placebo.

The imbalances in prognostic factors in the subgroup with known EGFR status are addressed by performing three Cox Proportional Hazard analyses each in the EGFR positive and negative subgroups. These three Cox Proportional Hazard analyses are for treatment alone, for treatment using the prerandomized stratification factors in the model and for treatment using all factors that were imbalanced between treatment groups in the model. This latter analysis is done with and without baseline alpha-1 acid glycoprotein (AAG) concentrations.

The favorable Tarceva survival effect is consistently seen in all analyses in the EGFR positive subgroup. In the EGFR negative subgroup the lack of Tarceva survival effect is consistent in the treatment only model (HR=1.01), in the model with treatment and all of the imbalanced factors (HR=1.03) and in the model with treatment and all of the imbalanced factors including AAG (HR=1.16). But in the model using treatment and the four prerandomization stratification factors, the HR is 0.93, indicating a possible small Tarceva survival effect in the EGFR negative subgroup.

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**Baseline Characteristics in EGFR Positive population:**

<b>Characteristic</b>	<b>Tarceva (N = 78)</b>	<b>Placebo (N = 49)</b>
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%)
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%)
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%)
2-3	26 (33.3%)	20 (40.8%)
No	36 (46.1%)	31 (63.3%)
Two	54 (69.2%)	31 (63.3%)
Prior Platinum: No	8 (10.3%)	5 (10.2%)
Yes	70 (89.7%)	44 (89.8%)

Imbalances in light and dark shade; dark favors Tarceva and light favors Placebo.

**Baseline Characteristics in EGFR Negative population:**

<b>Characteristic</b>	<b>Tarceva (N = 74)</b>	<b>Placebo (N = 37)</b>
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%)
Yes	53 (71.6%)	32 (86.5%)
Unknown	2 (2.7%)	0 (0.0%)
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%)
2-3	19 (25.7%)	6 (16.2%)
No	49 (66.2%)	21 (56.8%)
Two	44 (59.5%)	19 (51.3%)
Prior Platinum: No	2 (2.7%)	2 (5.4%)
Yes	72 (97.3%)	35 (94.6%)

Imbalances in light and dark shade; dark favors Tarceva and light favors Placebo.

**Survival Analyses Results in ITT Population--Cox Proportional Hazard**

**Cox's Proportional Hazard Model in the ITT Population  
Treatment Only in the Model**

ITT Population	Placebo N=243	Tarceva N=488	Hazard Ratio <sup>1</sup> (95% CI)	P-value <sup>2</sup>
# 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)		

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

**Cox's Proportional Hazard Model in the ITT Population Adjusting  
for Randomization Stratification Factors**

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 (yes vs. no)	1.534	1.123, 2.096	0.0071

\*P-value not adjusted for multiplicity; P-value by stratified log-rank for these factors was 0.0003; P-value by stratified log-rank including these stratification factors and EGFR status was 0.0002.

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**Survival Analyses Results in the EGFR Status Known Subgroup--  
Cox's Proportional Hazard**

**Cox's Proportional Hazard Model in EGFR Positive Population  
Treatment Only in the Model**

EGFR+ Population	Placebo N=49	Tarceva N=78	Hazard Ratio <sup>1</sup> (95% CI)	P-value <sup>2</sup>
# of Deaths	42	58	(0.430, 0.969)	0.0333
Med. Survival in months (95% CI)	3.8 (3.1, 6.8)	10.7 (7.9, 12.8)		

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

**Cox's Proportional Hazard Model in the EGFR Positive Population  
Adjusting for Randomization Stratification Factors**

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 Proportional Hazard Model in the EGFR Positive Population Adjusting for Randomization Stratification Factors**

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

**Cox's Proportional Hazard Model in the EGFR Positive Population  
Adjusting for Factors Which Appear to be Imbalanced**

<b>Covariates</b>	<b>Hazard Ratio</b>	<b>95% C.I.</b>	<b>P-value*</b>
Treatment (Tarceva vs Placebo)		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

**Cox's Proportional Hazard Model in the EGFR Positive Population  
Adjusting for Factors which Appear to be Imbalanced Including Base  
AAG**

<b>Covariates</b>	<b>Hazard Ratio</b>	<b>95% C.I.</b>	<b>P-value*</b>
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

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**Cox's Proportional Hazard Model in EGFR Negative Population  
Treatment Only in the Model**

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

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

**Cox's Proportional Hazard Model in the EGFR Negative Population  
Adjusting for Randomization Stratification Factors**

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

**Cox's Proportional Hazard Model in the EGFR Negative Population  
Adjusting for Randomized Stratification Factors**

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

**Cox's Proportional Hazard Model in the EGFR Negative Population  
Adjusting for Factors which Appear to be Imbalanced**

<b>Covariates</b>	<b>Hazard Ratio</b>	<b>95% C.I.</b>	<b>P-value*</b>
Treatment (Tarceva vs Placebo)		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

**Cox's Proportional Hazard Model in the EGFR Negative Population  
Adjusting for Factors which Appear to be Imbalanced Including AAG**

<b>Covariates</b>	<b>Hazard Ratio</b>	<b>95% C.I.</b>	<b>P-value*</b>
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

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**Cox's Proportional Hazard Analysis in Tarceva Treated Patients  
Receptor Status Only in the Model**

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

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

**Cox's Proportional Hazard Analysis in Placebo Treated Patients  
Receptor Status Only in the Model**

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

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

**Cox's Proportional Hazard Model in the EGFR Status Known  
Population—Treatment Only in the Model**

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

\*P-value not adjusted for multiplicity

**Cox's Proportional Hazard Model in the EGFR Status Known  
Population—Treatment and EGFR Status in the Model**

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

\*P-value not adjusted for multiplicity

**Cox's Proportional Hazard Model in the EGFR Status Known  
Population--Treatment, EGFR Status and Interaction in the Model**

<b>Covariates</b>	<b>Hazard Ratio</b>	<b>95% C.I.</b>	<b>P-value*</b>
Treatment (Tarceva vs Placebo)		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

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## Tumor Response

### TUMOR RESPONSE

RX	CR (%)	PR (%)	SD (%)
Tarceva N=427	4 (1)	34 (8)	150 (35)
Placebo N=211	1 (.5)	1 (.5)	56 (27)

CR + PR P= 0.0000 Fisher's Exact Test

CR + PR + SD P= 0.0000 Fisher's Exact Test

## Tumor Response By EGFR Status

### TARCEVA RESPONSE BY EGFR

EGFR	N = 427	CR or PR (%)	NO RESP (%)
Negative	62	2 (3)	60 (97)
Positive	69	8 (12)	61 (88)
Unknown	296	28 (9)	268 (91)

### TARCEVA EGFR BY RESPONSE

RESP	# RESP N=427	# EGFR Negative (%)	# EGFR Positive (%)	# UNKNOWN (%)
CR or PR	38	2 (5)	8 (21)	28 (74)
NO RESP	389	60 (15)	61 (16)	268 (69)

## Quality of Life Assessment

Please see the FDA statistical review and the FDA QOL consultation. See also the FAX sent to the Applicant on 10-15-04 detailing the reasons for not including the QOL results in the labeling.

The FDA statistical reviewer indicates the following:

Statistical Reviewer comments about the protocol and statistical analysis plan:

1. In the protocol (last amended on Nov 14, 2002), no specific items were identified as items of interest in the QoL measurement/analysis. It was stated that QoL will be assessed longitudinally and analysis of variance for repeated measure would be used for *domains* represented by aggregate scores.
2. The sponsor submitted a draft statistical analysis plan to the agency on October 17, 2002, which was subsequently discussed in a meeting on November 13, 2002. In this draft plan the sponsor for the first time specified that for the primary symptom benefit analysis, dyspnea, coughing and pain will be considered the three primary lung cancer symptoms. The draft plan further stated that the analyses of these symptoms will include estimation of the incidence (with 95% confidence intervals based on binomial distributions) of the individual symptoms (by grade) at baseline and by cycle, and comparisons between the treatment groups using chi-square test. It was further stated that additional analyses would include categorization of each symptom as improved, not changed, or deteriorated by cycle, and comparisons between treatment groups using chi-square tests; a third set of analyses would define an event as the worst severity grade or the presence of a new symptom, with time-to-event analyses using log-rank tests. In this submission, improvement, stable or worsening of symptoms were not defined. In this submission, the sponsor had asked the agency "Does the agency agree with the selection of dyspnea, cough and pain as the main disease related symptoms in the clinical benefit assessment?" The Agency's response was "Yes". This question did not address the actual measure or definition of endpoint for these 3 symptoms.
3. In this registration study, first patient was entered on November 1, 2001 and the last patient was entered on January 31, 2003. The sponsor submitted their final statistical analysis plan on June 18, 2003, 6 months after the last patient was entered on the trial. In this analysis plan for the first time the endpoint for the three symptom measurements was defined as the time to worsening, worsening defined as a 10 points or more decrement in the score from baseline. The agency did not comment on the choice of criteria for worsening or the endpoint at that time, as this was considered one among many secondary endpoints.

Statistical Reviewer comments about the analyses results:

1. The statistical reviewer conducted time to deterioration analyses in the other functional and symptom domains, global QoL scale and single items (a total of 26 identified measurements by the sponsor in the EORTC QLQ-C30 and QLQ-LC13 questionnaires). These results suggest that the time to deterioration in cough, dyspnea, and pain as presented by the sponsor are not robust/consistent as detailed below.
2. The physical functional domain and global QoL scale analysis suggest that the Tarceva treated group was worse than the placebo group (HR of 1.5 and 1.2 respectively). These are not consistent with the reported results for dyspnea and pain.
3. Although dyspnea as measured in QLQ-C30 single question was significantly better for Tarceva per sponsor analysis, the dyspnea domain (3 questions) as measured in QLQ-C13 was not significant (p-value = 0.3452).
4. Also, although pain as measured in QLQ-C30 single question was significantly better for Tarceva per sponsor analysis, chest pain as measured in QLQ-C13 was not significant (p-value = 0.06). It is also noted that Tarceva was worse for sore mouth and diarrhea.
5. The QoL analyses were based on the subgroup of patients who had baseline and at least one follow-up measurement (approximately 63% of the overall population for cough, 74% of the overall population for dyspnea and pain).

Clinical Reviewer comment about late protocol changes in statistical analysis :

Such late changes in statistical analysis plans are rare in academic clinical trials, but are almost routine in pharmaceutical company clinical trials for anticancer drugs. There is absolutely no justification for this. The FDA should not be in a position of having to make a decision on whether the company cheated when there is no way to find out and when such circumstances can be easily avoided. Although not specifically stated in the statistical review, the statistical reviewer has indicated orally that she recommends not including the QOL results in the Tarceva label.

Quality of Life Reviewer:

The QOL consultant recommends against including the QOL results in the labeling because definitions of the 3 symptoms selected by the Applicant for analysis (cough, dyspnea and pain) are inadequate. The standards in this study do not comply with standards for QOL in other parts of CDER.

She has also indicated orally that the QOL instruments are intended for use as a complete instrument and that an individual element of the instruments is not necessarily valid when used alone.

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## Summary of Efficacy

The following Modified Applicant Table summarizes the efficacy results.

	<b>TARCEVA N=488</b>	<b>Placebo N=243</b>	<b>p-value</b>
Median Survival 95% CI	7 months (5 to 7.8)	7 months (.1 to 6.3)	
Hazard Ratio* (Erlotinib: Placebo) 95% CI	0.73 0.60 to 0.87		0.001
Median Time to Deterioration in Cough*** 95% CI	28.1 weeks (16.1 to 40.0)	15.7 weeks (9.3 to 24.3)	0.041**
Median Time to Deterioration in Dyspnea*** 95% CI	20.4 weeks (16.3 to 28.3)	12.1 weeks (9.3 to 20.9)	0.031**
Median Time to Deterioration in Pain*** 95% CI	12.1 weeks (10.1 to 14.1)	8.1 weeks (7.7 to 12.3)	0.040**
Median Progression-free survival 95% CI	9.7 weeks (8.4 to 12.4)	8.0 weeks (7.9 to 8.1)	
Hazard Ratio * (Erlotinib: Placebo) 95% CI	0.61 0.51 to 0.73		<0.001
Objective Response Rate (CR+PR)	8.9%	0.9%	0.0000 <sup>1</sup>

\*Adjusted for stratification factors and HER1/EGFR status; a value less than 1.00 favors TARCEVA (primary analysis)

\*\*p-value adjusted for multiple testing

\*\*\*From the EORTC QLQ-C30 and QLQ-LC13 Quality of Life Questionnaires

<sup>1</sup> Fisher's Exact test

## Safety

The following Applicant Tables describe the drug exposure.

### Dose Intensity

		<b>Erlotinib (N=485)</b>	<b>Placebo (N=242)</b>
Dose intensity (mg/day)	Median	150	150
	Mean	138	146
	Range	44 - 152	83 - 153
Relative Dose intensity (%)	Median	100	100
	Mean	92	98
	Range	29 - 101	55 - 102

### Relative Dose Intensity

Relative Dose Intensity	n	Erlotinib (N=485)		Placebo (N=242)	
		(%)	n	(%)	n
>90%	376	(78)	226	(93)	
80-90%	23	(5)	7	(3)	
<80%	86	(18)	9	(4)	

### Summary of Exposure by Weeks of Treatment

Cumulative Calendar Weeks	n	Erlotinib (N=485)		Placebo (N=242)	
		(%)	n	(%)	n
<=4	84	(17)	41	(17)	
>4 - 8	110	(23)	86	(36)	
>8 - 16	118	(24)	60	(25)	
>16 - 26	60	(12)	30	(12)	
>26 - 52	82	(17)	22	(9)	
> 52	31	(6)	3	(1)	

The following Applicant Tables describe the dose reductions and dose interruptions and provide an overall summary of safety.

### Summary of Patients with Dose Reductions

	n	Erlotinib (N=485)		Placebo (N=242)	
		(%)	n	(%)	n
No Dose Reductions	391	(81)	238	(98)	
Dose Reduction to 100 mg	75	(15)	3	(1)	
Dose Reduction to 50 mg	19	(4)	1	(<1)	
Reason For Dose Reduction					
Rash	48	(10)	0	(0)	
Other Reason <sup>a</sup>	31	(6)	4	(2)	
Diarrhea	20	(4)	0	(0)	
Intercurrent Illness	4	(<1)	0	(0)	
Patient Missed Dose	3	(<1)	0	(0)	
Patient Request	1	(<1)	0	(0)	

### Summary of Patients with Dose Interruptions

	Erlotinib (N=485)		Placebo (N=242)	
	n	(%)	n	(%)
No Dose Interruption	185	(38)	122	(50)
Dose Interrupted for more than 7 consecutive days	105	(22)	26	(11)
Other reason <sup>a</sup>	38	(8)	5	(2)
Rash	35	(7)	0	(0)
Intercurrent illness	18	(4)	11	(5)
Diarrhea	9	(2)	0	(0)
Patient request	6	(1)	3	(1)
Patient missed dose	4	(<1)	1	(<1)
Patient non-compliance	4	(<1)	4	(2)
Administrative	2	(<1)	3	(1)
Not applicable	1	(<1)	0	(0)
Dose Interrupted for more than 14 consecutive days	38	(8)	10	(4)
Rash	15	(3)	0	(0)
Other reason <sup>b</sup>	12	(2)	3	(1)
Diarrhea	3	(<1)	0	(0)
Intercurrent illness	3	(<1)	5	(2)
Patient request	2	(<1)	1	(<1)
Patient missed dose	1	(<1)	0	(0)
Patient non-compliance	1	(<1)	1	(<1)
Administrative	0	(0)	1	(<1)

### Overall Summary of Safety

	Erlotinib (N=485)		Placebo (N=242)	
	n	(%)	n	(%)
Patients with at least one AE	481	(99)	233	(96)
Patients with at least one treatment-related AE	411	(85)	123	(51)
AEs Regardless of Causality by worst severity				
Grade 1	22	(5)	27	(11)
Grade 2	157	(32)	65	(27)
Grade 3	195	(40)	87	(36)
Grade 4	107	(22)	54	(22)
Treatment-Related AEs by worst severity				
Grade 1	95	(20)	68	(28)
Grade 2	202	(42)	41	(17)
Grade 3	98	(20)	12	(5)
Grade 4	16	(3)	2	(<1)
Patients with at least one SAE	165	(34)	68	(28)
Patients with at least one treatment-related SAE	41	(8)	7	(3)
Patients who discontinued study due to treatment-related AEs	26	(5)	4	(2)
Patients who died on treatment or within 30 days	155	(32)	71	(29)
Patients who died due to a treatment-related AE	4	(<1)	1	(<1)

Dose reduction to 100 mg occurred in 15% of erlotinib patients and further reduction to 50 mg in 4% of patients, compared with 1% and < 1% in placebo patients. Discontinuation due to protocol toxicity occurred in 5% in the erlotinib group and 2% in the placebo group.

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

Rash (75% vs 17%) and diarrhea (54% vs 18%) in the Erlotinib and Placebo group respectively were the most common AEs regardless of causality. Most were Grade 1 and 2 in severity and manageable without intervention. Severe rash occurred in 9% and severe diarrhea occurred in 6% of erlotinib-treated patients and each resulted in study discontinuation in 1%. Dose reductions were required for 10% of patients with rash and 4% of patients with diarrhea.

The incidence of ILS was 0.8% in both the erlotinib and placebo groups.

There was no apparent hematological toxicity associated with erlotinib therapy. The possibility of an interaction between erlotinib and warfarin was monitored in patients on 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  $\geq$  4) were seen in 26% vs 21% of warfarin-treated patients in the erlotinib and placebo groups, respectively. Whether patients received warfarin or not, reports of clinically recognized bleeding occurred in 24% of erlotinib treated patients compared to 17% with placebo. Most were inconsequential Grade 1 episodes of hemoptysis and epistaxis. Severe bleeding cases include 8 erlotinib patients (2%) with serious gastrointestinal hemorrhage and none in placebo patients. Concurrent warfarin administration was present in 2 of these 8 patients and other medications (ie, NSAID) contributed as well.

Eye disorders were more frequent in the erlotinib arm (27% vs 9%). Most were conjunctivitis and keratoconjunctivitis sicca (dry eyes) experienced by 12% each of the erlotinib patients compared with 2% and 3%, respectively, in the placebo patients. The worst severity was Grade 3 occurring in < 1% in each arm. Keratitis was reported in 3% of erlotinib patients compared with 1% of placebo patients. All except one case was less than Grade 2 and none were reported as medically significant or resulting in discontinuation of protocol therapy. Concomitant ophthalmological preparations such as artificial tears were administered to 11% of the patients in the erlotinib group and 1% in the placebo group.

## CONCLUSIONS

In a randomized placebo controlled double blind trial in a total of 731 patients with NSCLC after failure of one or two prior chemotherapy regimens, Tarceva has a favorable effect on survival, PFS and tumor response.

Tarceva was designed to inhibit tyrosine kinase by targeting the EGF receptor. Thus there is great interest in whether Tarceva treatment effect is impacted by EGFR status. Assessment of the effect of EGFR status on Tarceva efficacy is limited because only 33% of study patients have

known EGFR status. Subgroup univariate analyses in the 238 (33% ) patients with known EGFR status indicate that Tarveva clearly prolongs survival in EGFR positive patients (median Tarveva 10.7 mo vs Placebo 3.8 mo, HR= 0.646). In EGFR negative patients there is no apparent Tarveva effect on survival (median Tarveva 5.4 mo vs Placebo 7.5 mo, HR = 1.01). However, the 95% confidence intervals are wide and overlap for the EGFR positive and negative subgroups. Thus a favorable Tarveva survival effect in the EGFR negative subgroup can not be excluded with certainty.

A conclusion that Tarveva is not beneficial in receptor negative patients would cut the Applicant's market in half. About half of study patients with known receptor status are receptor negative. The Applicant has a strong disincentive to provide information on patient receptor status and has argued forcefully in this application that receptor status is not important. This is an emerging problem that we have seen in at least one other NDA for a targeted anticancer therapy. The FDA must work proactively to assure that this important information is publically available for this drug and for future targeted drugs.

Tarveva safety is better than most alternative therapies and is acceptable in view of its efficacy.

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## RECOMMENDATIONS

This NDA should be approved for the following indication.

"For treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen."

Labeling revisions are required. Please see revised package insert with input from all of the Tarceva review team disciplines.

The Applicant should make a Phase 4 commitment to assess the relation of EGFR status to efficacy in ongoing and future studies. It is obvious that this will occur only if known EGFR status (or tissue suitable and available for its determination) is a study eligibility requirement.

**/S/**

John R. Johnson, M.D.  
October 21, 2004

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