Title

Randomized, Open-label Phase II Clinical Trial of Combination Erlotinib (Tarceva®) and Fulvestrant (Faslodex®) versus Erlotinib (Tarceva®) Alone in Advanced or Metastatic Non-Small Cell Lung Cancer Patients

Author

Garon, Edward

Publication Date

2014

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA
Los Angeles

Randomized, Open-label Phase II Clinical Trial of Combination Erlotinib (Tarceva®) and Fulvestrant (Faslodex®) versus Erlotinib (Tarceva®) Alone in Advanced or Metastatic Non-Small Cell Lung Cancer Patients

A thesis submitted in partial satisfaction
of the requirements for the degree Master of Science
in Clinical Research

by

Edward Garon

2014

ABSTRACT OF THE THESIS

Randomized, Open-label Phase II Clinical Trial of Combination

Erlotinib (Tarceva®) and Fulvestrant (Faslodex®) versus Erlotinib (Tarceva®) Alone

in Advanced or Metastatic Non-Small Cell Lung Cancer Patients

by

Edward Garon

Master of Science in Clinical Research

University of California, Los Angeles, 2014

Professor Robert M. Elashoff, Chair

Purpose

This randomized, open-label trial evaluated erlotinib, an inhibitor of human epidermal growth factor receptor (EGFR), and a combination of erlotinib with fulvestrant, an anti-estrogen, in patients with advanced non-small cell lung cancer (NSCLC).

Patients and Methods

Patients with NSCLC were randomly assigned at a ratio of 2:1 to receive erlotinib plus fulvestrant or erlotinib. Eligibility requirements included ECOG performance status 0-2, no prior EGFR-directed therapy, and previous treatment with one or more chemotherapy regimens unless patient refused. Primary end point was objective tumor response rate; additional endpoints included overall survival (OS), progression free survival (PFS) and safety.

Results

106 patients were randomized and 100 patients (evaluated population) received at least one dose of study drug. The overall response rate (RR) for the cohort was 20.7%: 14.3% in erlotinib arm and 24.3% in erlotinib plus fulvestrant arm. Median PFS was 1.8 months for erlotinib and 1.9 for

erlotinib plus fulvestrant (HR=.85, 95% CI, .55-1.33, and p=0.47). Median OS was 5.7 months for erlotinib versus 9.4 months for erlotinib plus fulvestrant (HR=0.96, 95% CI, 0.6 to 1.55, and p=0.88). Response rate was significantly correlated with EGFR mutational status (p<0.0001). For patients with wild-type EGFR, clinical benefit rate (CBR: partial response + stable disease) was 54.8% with erlotinib plus fulvestrant versus 8.3% with erlotinib (p=0.0056). Common treatment-related adverse events were dermatological and gastrointestinal, predominantly grade 1 to 2.

Conclusion

We were not able to demonstrate superiority of erlotinib with fulvestrant with respect to objective tumor response, OS and PFS compared to erlotinib alone. As anticipated, EGFR mutations were strongly associated with favorable outcomes. Within the EGFR wild-type subset, CBR was superior in the combination arm, although this was a post-hoc analysis rather than a prospective secondary endpoint. Ongoing work is evaluating blood and tissue samples from study participants in an attempt to identify biomarkers with anti-estrogens.

ClinicalTrials.gov: NCT00100854

The thesis of Edward Garon is approved.

_____
Steven Dubinett

_____
Elliot M Landaw

_____
Robert Elashoff, Committee Chair

University of California, Los Angeles

2014

Table of Contents

ACKNOWLEDGMENTS

Co-authors:

Steven M. Dubinett[1], Robert M. Elashoff[1], Jill M. Siegfried[2]. David J. Park[3], Rupesh J. Parikh[4], Ravi Patel[5], Eddie H. Hu[6], Karen L. Reckamp[7], Brad Adams[1], Diego Martinez[1], He-Jing Wang[1], Fairooz Kabbinavar[1], Sanja Dacic[2], Meghan Brennan[1], Isett Laux[8], Diana C. Marquez-Garban[1], Laura P. Stabile[2], Brian Wolf[1], Dennis J. Slamon[1], and Richard J. Pietras[1]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA;

[2]University of Pittsburgh Cancer Institute, Pittsburgh, PA;

[3]St. Jude Heritage Medical Group, St. Jude Crosson Comprehensive Cancer Center, Fullerton, CA;

[4]Comprehensive Cancer Care Centers of Nevada, Las Vegas, NV;

[5]Comprehensive Blood and Cancer Center, Bakersfield, CA;

[6]Central Heme/Onc Medical Group, Alhambra, CA;

[7]City of Hope, Duarte, CA;

[8]Translational Research in Oncology- United States, Los Angeles, CA.

Funding Provided By: 1K23CA149079, P50 CA090440, V Foundation for Cancer Research, Jonsson Comprehensive Cancer Center, Wolfen Family Lung Cancer Research Program, Stiles Program in Oncology, National Lung Cancer Partnership and One Ball Matt Memorial Golf Tournament

Additional thanks to the study staff and investigators at all sites, as well as the patients and their families.

CHAPTER 1: THESIS BODY

Introduction

Lung cancer is the leading cause of cancer death in the United States, and is responsible for more deaths each year than colon, breast, and prostate cancer combined (1). Due to mutations leading to increased growth factor signaling, EGFR has been implicated in lung cancer pathogenesis (2). Treatment with erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, improves overall survival in patients with recurrent NSCLC (3). Compared to chemotherapy with carboplatin–paclitaxel, treatment with the EGFR inhibitor gefitinib increased progression-free survival (PFS) in patients with untreated NSCLC with EGFR-activating mutations (4). However, the evaluation of potential mechanisms of resistance and investigation of its activity with other agents warrant further exploration.

Several studies suggest the role of estrogens in carcinogenesis and progression, as evident in estrogen receptor-α (ER-α) and ER-β mRNA and protein expression in malignant lung epithelial cells (5). Postmenopausal hormonal use has also been associated with increased mortality after diagnosis of lung cancer (6). Fulvestrant, a pure antiestrogen that downregulates ER in target tissues, is approved for the treatment of progressive breast cancer (7-9).

Details of the interactions between EGFR and the estrogen receptor pathway have begun to emerge. ER may mediate gene transcription by integrating signals from EGFR-activated pathways as well as from steroid binding (10). It has been reported that the combination of gefitinib and the antiestrogen, fulvestrant, resulted in an additive antitumor effect in ER positive breast cancer cell lines (11). As a result, there may be potential for use of EGFR tyrosine kinase inhibitors combined with anti-hormone agents to treat NSCLC. Therefore, we conducted an

open-label, randomized, phase II study in patients with advanced NSCLC evaluating erlotinib versus erlotinib plus fulvestrant.

Patients and Methods

Patient Population

Key inclusion criteria included age ≥ 18 years, pathologically proven advanced (Stage IIIb or IV) NSCLC, previously treated with one or more regimens or refusal or inability to receive standard chemotherapy, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2, measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.0), fresh or archival tumor tissue availability at baseline, and adequate organ function. Exclusion criteria included chemotherapy or non-cytotoxic investigational agents within 4 weeks of initiating treatment, prior history of EGFR inhibitor or anti-estrogen for the treatment of cancer, active CNS metastasis, and any significant condition that could impede with participation.

Trial Design and Treatment

This multicenter, randomized, open-label phase II trial compared the objective tumor response rate (ORR) as defined by RECIST 1.0 in erlotinib and erlotinib/fulvestrant treatment arms. Secondary endpoints included characterization of the toxicities and the ability to deliver maximal doses of both agents, as well as identification of patient subgroups that are distinct with respect to response and toxicity.

Patients were randomly assigned (1:2) to receive oral erlotinib (150mg once daily) or erlotinib (150mg once daily) plus fulvestrant (500 mg IM loading dose on day 1 and 15 of cycle 1 and then day 1 of subsequent cycles). Patients were assessed in 28-day cycles. One dose reduction (100 mg) was permitted for erlotinib and no dose reductions for fulvestrant were allowed. For an intolerable grade 3 or 4 rash, erlotinib dose reduced to 100 mg qday when rash

resolved to < grade 2; if possible, original dose was reinstated if there was no further toxicity for an entire cycle at reduced dose. Suggested measures for management of skin toxicity included topical or systemic antibiotics, along with topical or a short course of systemic corticosteroids. Treatment was continued until documented progression, unacceptable toxicity, withdrawal of consent, or death.

Assessments

During the study, tumor measurement and survival status were collected for evaluation of ORR which was the primary endpoint, as well as progression-free survival (PFS) and overall survival (OS) which were secondary endpoints. Each of these endpoints was analyzed in both arms individually, as it was a non-comparative study. Computed tomography (CT) scans were obtained at baseline and every two cycles (8 weeks). The investigator assessed disease status per RECIST 1.0. Patients were also monitored for adverse events (AEs), changes in laboratory values and physical examination findings.

Evaluation of Safety and Tolerability

Safety and tolerability were assessed during the trial (from initiation of study treatment until at least 30 calendar days after the last dose of study drug) by standard monitoring and methods.

Determination of EGFR Status and Biomarker Correlates

Tumor tissue, prior to the first dose, was obtained in order to enroll patients in this study. If normal adjacent lung tissue was not available, the patient was still eligible to participate in this study given other eligibility met protocol requirements. The tumor samples were either a tissue block (1mm; 10% neutral buffered formalin; paraffin embedded) or 20 optimal (but at least 5) unstained slides that are 4-5 micron thick sections (formalin fixed, paraffin-embedded tissue).

The pre-treatment tissue samples are currently being evaluated for ER-α, ER-β and progesterone receptor (PR), as well as several exploratory biomarkers. In addition, we sequenced for mutations in the EGFR tyrosine kinase domain (exons 18-21) on available tissue samples. Any EGFR result in which exon 19 and 21 were sequenced was considered informative. Whole blood sample was obtained at C1D1 for genomic DNA analysis, which will be performed by evaluating EGFR CA repeat and polymorphisms. Plasma and serum samples were obtained at the start of therapy (C1D1) and values will be compared to C2D1 and C3D1 samples to evaluate estrogen (estrone and estradiol) levels as well as exploratory biomarkers.

Statistical Rationale for Study Design and Statistical Analyses

The study enrolled 106 subjects in a 2:1 ratio to the fulvestrant plus erlotinib combination: erlotinib monotherapy arms, respectively. Details of the power calculations are discussed in chapter 2. The primary end-point of this study was the objective response rate in each arm, and the erlotinib plus fulvestrant arm was to be compared to the 10% rate for erlotinib alone from studies in the literature. The protocol itself does not call for any comparative analysis between the two treatment arms. However, we have looked at between arm differences. (see Chapter 2). In analyzing the data, we have performed an exploratory analysis comparing the two treatment arms. Response rate, clinical benefit rate (partial response plus stable disease) and a variety of clinical factors present at baseline by arm were analyzed using a Chi-Square test. Median PFS and OS were estimated from Kaplan-Meier curves. Stratified log-rank test was used to test the difference in PFS and OS between treatment arms.

Results

Patient Characteristics

Between March 2006 and June 2011, 106 patients were randomly assigned to receive erlotinib (n=33) or erlotinib plus fulvestrant (n=73) at the University of California, Los Angeles

and through the Translational Oncology Research Institute (TORI) network, according to a pre-specified randomization algorithm (Table 1). To account for dropouts, this was four patients more than the original number based on our power calculations. However, six patients withdrew prior to initiation of therapy for a total of 100 treated subjects. Randomization was stratified according to gender and performance status. Baseline characteristics were well balanced between the two treatment groups, with the exception that the erlotinib group had higher lymph node metastasis rate, compared with the erlotinib plus fulvestrant group (two sided p=.0085; Table 2). 69 participants had EGFR status (mutant or wild type) determined. 33.3% of female participants were EGFR mutant versus 8.3% of males (chi-square test p=0.0217).

Efficacy

The overall response rate (RR) in the entire cohort was 20.7%: 14.3% in erlotinib arm and 24.3% in erlotinib plus fulvestrant arm. The best response rate for patients receiving study treatment showed no significant difference between erlotinib and erlotinib plus fulvestrant (chi square p=0.47). As anticipated, when comparing mutant and wild-type EGFR participants, RR was significantly correlated with mutant EGFR status (two-sided p<0.0001) with superior response in EGFR mutant patients. This is based on 69 subjects for whom EGFR status could be assessed, 17 patients with mutations and 52 without mutations (wild type). Most EGFR mutant patients responded to therapy without clear differences being seen between the arms in this small subset. For patients with wild-type EGFR, a significant difference was seen for CBR (best response of partial response or stable disease), 54.8% with erlotinib plus fulvestrant versus 8.3% with erlotinib (p=0.0056). This is based on analysis of the 52 EGFR wildtype subjects. 12 of the 13 erlotinib alone subjects could be assessed for outcome, with 11 of 12 having progressive disease as the best outcome, and stable disease seen in the remaining subject. 31 of the 39 EGFR

wildtype subject could be assessed for outcome with 3 partial responses, and 14 subjects each with stable disease and progressive disease as their best response.

PFS was analyzed when 90 events had occurred. At time of analysis, 79 deaths had occurred (26 patients receiving erlotinib, 53 receiving erlotinib plus fulvestrant). Overall, the median PFS was 1.8 months for erlotinib and 1.9 months for erlotinib plus fulvestrant (hazard ratio [HR] = 0.85, 95% CI, 0.55-1.33, two-sided p=0.47 based on a log-rank test; Figure 1A). The median OS was 5.7 months for erlotinib vs. 9.4 months for erlotinib plus fulvestrant; (HR=0.96, 95% CI, 0.6 to 1.55, two sided p=0.88 based on a log rank test; Figure 1B).

For the EGFR mutant subset, median PFS was 16.4 months, compared to 1.8 months for wild-type EGFR (HR=0.19, 95% CI, 0.08-0.41; two-sided p<0.0001; Figure 1C). Median OS for the EGFR mutant subset was 27.9 months, compared to 5.8 months for the wild-type subjects (HR=0.23, 95% CI, 0.11-.49; two-sided p<0.0001; Figure 1D). The number of EGFR mutant patients was two small to make between arm comparisons. Within the EGFR wild-type subset, a trend toward favorable OS with erlotinib plus fulvestrant was noted (median OS 7.4 months for erlotinib + fulvestrant vs. 4.9 months for erlotinib; HR = 0.69, 95% CI, 0.36-1.31, two sided p=0.25 based on a log rank test).

When analyzing gender, the median PFS was 1.7 months for men versus 3.3 months for women (HR=1.74, 95% CI, 1.14-2.66, two-sided p=0.0078 based on a log-rank test; Figure 1E). The same trend was noted for OS with median OS 11.2 months for females vs. 6.1 months for males (HR: 1.39, 95% CI: 0.89-2.17, two sided p=0.14; Figure 1F). It is likely that this difference based on gender was largely related to the difference in the frequency of EGFR mutations.

Safety and Tolerability

The most common AEs (all grades) in the evaluable population (n=100) were pain (42.4% vs. 47.8%), rash (48.5% vs. 61.2%), diarrhea (42.4% vs. 38.8%), and fatigue (33.3% vs. 37.3%) for erlotinib versus erlotinib plus fulvestrant, respectively (Table 3). There were no significant differences between arms. The majority of the events were of grade 1 or 2 severity and manageable with standard supportive care.

Grade 3-4 AEs comprised dyspnea, pain, infection and rash. A total of 43 patients experienced 99 grade 3-4 AEs; 9 patients in erlotinib group had 24 grade 3-4 AEs and 34 patients in erlotinib plus fulvestrant group had 75 grade 3-4 AEs. Two deaths occurred during the study, one due to cardiac-ischemia/infarction in the erlotinib group and one due to respiratory failure in the erlotinib plus fulvestrant group. Neither was felt to be drug-related.

Discussion

This open-label, randomized trial examined the efficacy and safety of erlotinib in combination with the anti-estrogen fulvestrant compared to erlotinib alone for advanced NSCLC in the 100 patients who received study treatment. There was no demonstration of improved PFS or OS after treatment with erlotinib and fulvestrant over treatment with erlotinib (HR=.85, two sided P=0.47; HR=.96, two sided p=0.88). Yet, based on prior statistical analysis, the clinical results of a 24.3% RR did detect a greater than 100% improvement in RR with the combination of fulvestrant and erlotinib, compared to historical data for erlotinib monotherapy. This was likely driven in part by a higher percentage of patients with EGFR mutant tumors than would be seen in a typical unselected patient population (see Chapter 2). This suspicion is supported by the finding that the control arm (erlotinib alone) also performed better than historical controls with respect to the primary endpoint of response rate.

Estrogen stimulates NSCLC gene expression, induces proliferation and growth, and diminishes apoptosis (5, 12-13). Notably, these processes can be prevented through the use of anti-estrogens in pre-clinical models. Relevant to the process of lung cancer progression, estrogens stimulate NSCLC cell proliferation *in vitro* and tumor growth *in vivo*; these actions are inhibited by the antiestrogen fulvestrant (14). Prior work has noted that estrogen significantly increases NSCLC proliferation in the presence of either ER-α and ER-β (15). These results support the present trial.

At the time the study was initiated, the correlation between EGFR status and treatment was not known. Consistent with previous reports, response to erlotinib was significantly associated with EGFR status in our study (16-17). Prior studies have shown that erlotinib in combination with other therapies may or may not yield an additive effect (18-21). In the present trial, the OS and PFS for patients with an EGFR mutation were similar between the two treatment arms; however, due to the small sample size, the stratified log-rank test cannot be deemed accurate.

A trend toward improved RR, OS, and PFS with erlotinib plus fulvestrant relative to erlotinib for patients with an EGFR wild-type status was observed, but did not reach statistical significance. Among the 100 patients who received study treatment, 69 were ascribed an EGFR status. Within the EGFR wild type group, the CBR rate favored the erlotinib plus fulvestrant arm. A recent study that evaluated 54 NSCLC cell lines for growth inhibition with EGFR inhibitors, antiestrogen treatment, or the combination, recognized that fulvestrant has modest single agent activity in vitro and adds to effects of EGFR inhibitors, including synergy in the EGFR-mutant, erlotinib-resistant H1975 line (22). Ongoing work is evaluating blood and tissue samples from study participants to evaluate biomarkers related to ER and EGFR gene expression to correlate

with clinical response. Further investigation into the effects of fulvestrant, not in combination with erlotinib, in EGFR wild type patients is warranted.

A phase I dose escalation study of carboplatin, pemetrexed and exemestane, an aromatase inhibitor, in postmenopausal women with metastatic non-squamous NSCLC is currently underway. The preference towards postmenopausal women stems from studies that showed an increased incidence and mortality risk from lung cancer among postmenopausal women who were actively on hormone replacement therapy, as well as the restriction of exemestane efficacy to post-menopausal women (25-26). To select well-matched patients in the future, prescreening NSCLC patients (i.e., high estrogen or ER expression in tumor cells) may help select those most likely to respond to antiestrogens and aromatase inhibitors, but these findings will require validation with our ongoing biomarker analysis.

References

1. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ: Cancer statistics, 2003. CA Cancer J Clin 2003;53:5-26.

2. Sharma SV, Bell DW, Jeffrey Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nature Reviews Cancer 2007;*7*:*169-181*.

3. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P, Seymour L. Erlotinib in previously treated non-small-cell lung cancer.. N Engl J Med. 2005;353(2):123-32.

4. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-57.

5. Stabile LP, Davis AL, Gubish CT, Hopkins TM, Luketich JD, Christie N, et al. Human non-small cell lung tumors and cells derived from normal lung express both estrogen receptor alpha and beta and show biological responses to estrogen. Cancer Res. 2002;62:2141-50.

6. Chlebowski RT, Anderson GL, Manson JE, Schwartz AG, Wakelee H, Gass M, Rodabough RJ, Johnson KC, Wactawski-Wende J, Kotchen JM, Ockene JK, O'Sullivan MJ, Hubbell FA, Chien JW, Chen C, Stefanick ML. Lung cancer among postmenopausal women treated with estrogen alone in the women's health initiative randomized trial. J Natl Cancer Inst. 2010 Sep 22;102(18):1413-21.

7. Robertson JF, Nicholson RI, Bundred NJ, Anderson E, Rayter Z, Dowsett M, Fox JN, Gee JM, Webster A, Wakeling AE, Morris C, Dixon M. Comparison of the short-term biological effects of 7α-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5,(10)-triene-3, 17β-diol (FVT) versus tamoxifen in postmenopausal women with primary breast cancer. Cancer Res 2001;18:6739-6746.

8. Osborne DK, Pippen J, Jones SE, Parker LM, Ellis M, Come S, Gertler SZ, May JT, Burton G, Divery I, Webster A, Morris C, Elledge R, Buzdar A. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus ANZ in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 2002;20:3386-3395.

9. Howell A, Robertson JF, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg UR, Bergote I, Erikstein B, Webster A, Morris C. Fulvestrant, formerly CI 182, 780, is as effective as ANZ in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 2002;20:3396-3403.

10. Pietras RJ, Nemere I, Szego CM. Steroid hormone receptors in target cell membranes. Endocrine 2001;14:417-427.

11. Okubo S, Kurebayashi J, Otsuki T, Yamamoto Y, Sonoo H. Additive antitumour effect of the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa, ZD 1839) and the antioestrogen fulvestrant (Faslodex, ICI 182,789) in breast cancer cells. Brit J Cancer 2004;90:236-244.

12. Pietras RJ, Marquez DC, Chen HW, Tsai E, Weinberg O, Fishbein M. Estrogen and growth factor receptor interactions in human breast and non-small cell lung cancer cells. Steroids. 2005;70:372-81.

13. Stabile LP, Siegfried JM. Estrogen receptor pathways in lung cancer. Curr Oncol Rep. 2004;6:259-67.

14. Brodie A. Aromatase inhibitor development and hormone therapy: a perspective. Semin Oncol. 2003;30:12-22.

15. Niikawa H, Suzuki T, Miki Y, Suzuki S, Nagasaki S, Akahira J, et al. Intratumoral estrogens and estrogen receptors in human non-small cell lung carcinoma. Clin Cancer Res. 2008;14:4417-26.

16. Zhou C, Wu Y-L, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12: 735–42.

17. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-246.

18. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2005;23:5892-5899

19. Spigel DR, Burris HA, Greco FA, et al. Randomized, double-blind, placebo-controlled, phase II trial of sorafenib and erlotinib or erlotinib alone in previously treated advanced non-small-cell lung cancer. J Clin Oncol 2011; 29:2582–2589.

20. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small cell lung cancer: the Tarceva Lung Cancer Investigation Trial. J Clin Oncol 2007;25:1545-1552

21. Scagliotti GV, Krzakowski M, Szczesna A,et al. Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non-small-cell lung cancer: a phase III trial. J Clin Oncol 2012; 30: 2070–2078.

22. Garon EB, Pietras RJ, Finn RS, Kamranpour N, Pitts S, Márquez-Garbán DC, Desai AJ, Dering J, Hosmer W, von Euw EM, Dubinett SM, Slamon DJ. Antiestrogen fulvestrant enhances the antiproliferative effects of epidermal growth factor receptor inhibitors in human non-small-cell lung cancer. J Thorac Oncol. 2013;8(3):270-8.

23. Raso, M; Behrens, C; Herynk, MH; Liu, S; Prudkin, L; Ozburn, NC; Woods, DM; Tang, X; Mehran, RJ; Moran, C; et al. Immunohistochemical expression of estrogen and progesterone receptors identifies a subset of NSCLCs and correlates with EGFR mutation. Clin. Cancer Res. 2009, 15, 5359–5368.

24. Mollerup S, Jorgensen K, Berge G, Haugen A. Expression of estrogen receptors α and β in human lung tissue and cell lines. Lung Cancer 2002;37:153–9.

25. Stabile LP, Lyker JS, Gubish CT, Zhang W, Grandis JR, Siegfried JM. Combined targeting of the estrogen receptor and the epidermal growth factor receptor in non-small cell lung cancer shows enhanced antiproliferative effects. Cancer Res. 2005;65:1459-70.

26. Traynor AM, Schiller JH, Stabile LP, Kolesar JM, Eickhoff JC, Dacic S, et al. Pilot study of gefitinib and fulvestrant in the treatment of post-menopausal women with advanced non-small cell lung cancer. Lung Cancer. 2009;64:51-9.

Figures & Tables

Table 1. Site Distribution

Site Location	Erlotinib Alone	Erlotinib plus Fulvestrant	Total
Alhambra	1	5	6
Bakersfield	5	5	10
Fullerton	4	14	18
Inland Valleys	1	1	2
Las Vegas	2	6	8
Long Beach	1	4	5
Northridge	0	3	3
Redondo Beach	1	4	5
Santa Maria	3	2	5
Terre Haute	1	0	1
UCLA	10	23	33
UCLA Santa Monica	3	4	7
UCLA Westlake	1	2	3
Total	33	73	106

This multicenter phase II trial enrolled subjects at the University of California, Los Angeles and through the Translational Oncology Research Institute (TORI) network.

Table 2. Patient Baseline Characteristics (n=106)

Patients Characteristics	Erlotinib alone (n=33)	Erlotinib + Faslodex (n=73)	Total (n=106)
Age mean ± SD	68.2 ± 11.6	67.9 ± 10.6	68.0 ± 10.9
Median, min - max	66, 42-87	68, 37-89	68, 37-89
Gender			
F	18 (54.5)	43 (58.9)	61 (57.6)
M	15 (45.5)	30 (41.1)	45 (42.4)
Ethnicity			
Asian	7	17	24
Black	2	3	5
Hispanic	5	6	11
White	18	46	64
White/Hispanic	1	0	1
Other(Filipino)	0	1	1
ECOG			
0	13 (39.4)	29 (39.7)	42 (39.6)
1	15 (45.4)	35 (48.0)	50 (47.2)
2	5 (15.2)	9 (12.3)	14 (13.2)
Smoker	26 (78.8)	53 (72.6)	79 (74.5)
Histologic Grade			
G1	5	7	12
G2	12	9	21
G3	7	31	38
G4	0	2	2
GX	5	18	23
missing	4	6	10
T-stage			
T1	7	6	13
T2	13	17	30
T3	1	11	12
T4	12	32	44
TX	0	7	7
N-Stage			
N0	4	14	18
N1	6	6	12
N2	7	25	32
N3	12	15	27
NX	4	13	17
M-Stage			
M0	7	24	31
M1	25	44	69
MX	1	4	5
missing	0	1	1
Stage at Dx			
I	4	4	8
II	1	3	4
III	4	20	24
IV	24	45	69
unknown	0	1	1
Stage at study enrollment			
IIIB	1 (3.0)	11 (15.1)	12 (11.3)
IV	32 (97.0)	62 (84.9)	94 (88.7)
Previous treatment			
surgery	8 (24.2)	17 (23.3)	25 (23.6)
chemo	23 (69.7)	57 (78.1)	80 (75.5)
XRT	18 (54.6)	32 (43.8)	50 (47.2)
Metastasis			
Bone metastasis	17 (51.5)	29 (39.7)	46 (43.4)
Lymph	28 (84.8)	43(58.9)	71(67.0)
Bone marrow	0	1	1
Liver	9 (27.3)	15 (20.6)	24 (22.6)
GI	2	1	3
other	17	39	56
(in “other” category			
Lung	6	15	
Brain	3	10	
Adrenal gland)	5	7	
Current CNS metastasis	4 (12.1)	10 (13.7)	14 (13.2)
EGFR			
Mutant	7	10	17
Wild type	13	41	54
Not done	13	22	35

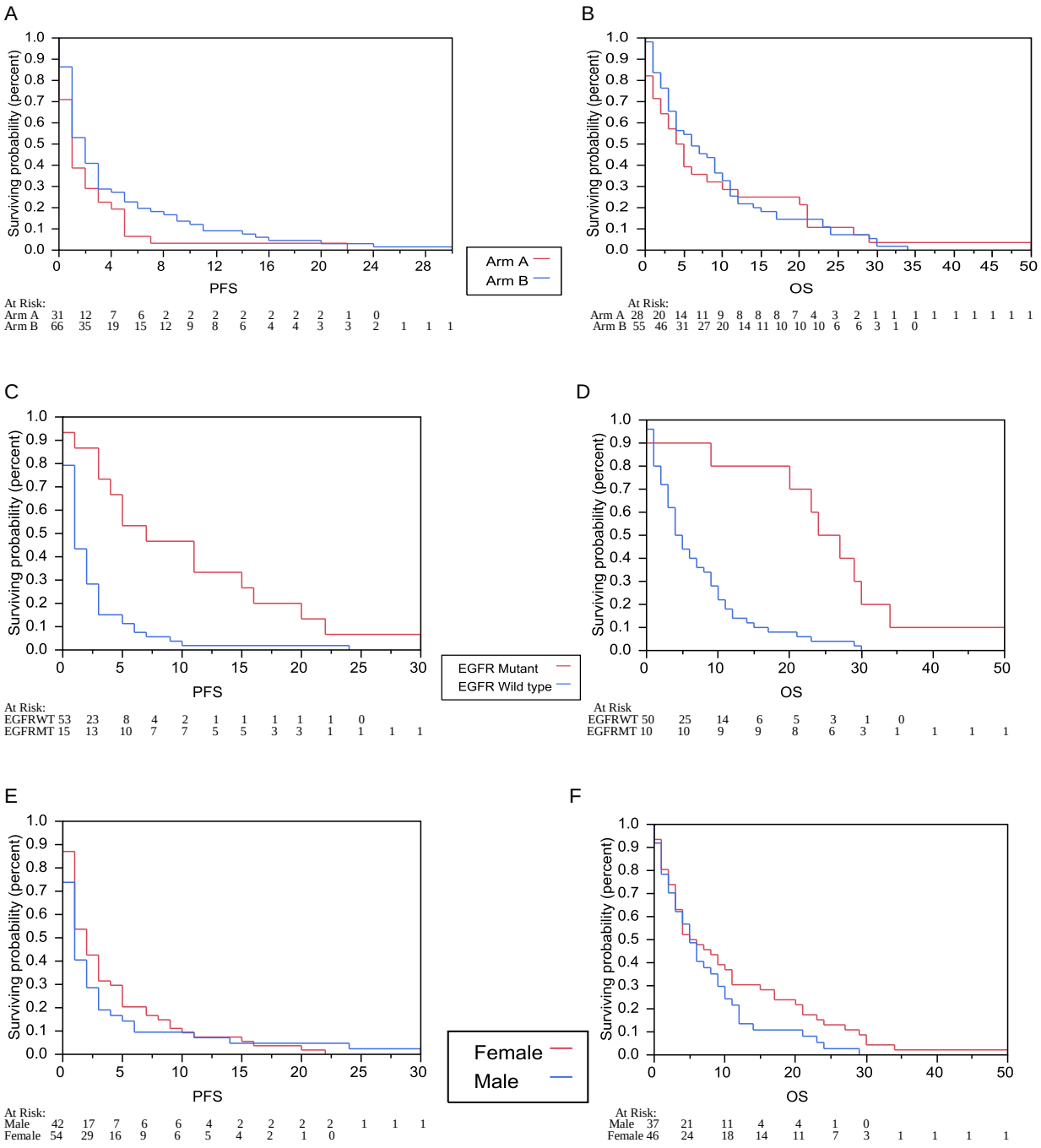

Figure 1. Kaplan Meier estimates of (A, C, E) progression-free survival and (B, D, F) overall survival outcomes in (A, B) intent-to-treat, (C, D) EGFR mutant v. EGFR wildtype, and (E, F) male v. female populations. All time endpoints above are measured in months.

Table 3. Most Frequent Treatment-Related Adverse Events Occurring in ≥10% patients in Each Treatment Arm

Adverse Event	Erlotinib alone (n=33)		Erlotinib + Faslodex (n=67)	
	# Episodes	# Pts (%)	# Episodes	# Pts (%)
Pain	30	14 (42.4)	77	32 (47.8)
Rash	31	16 (48.5)	74	41 (61.2)
Diarrhea	19	14 (42.4)	45	26 (38.8)
Fatigue	13	11 (33.3)	32	25 (37.3)
Anorexia	9	8 (24.2)	29	21 (31.3)
Dyspnea	10	6 (18.2)	26	22 (32.8)
Dry skin	13	10 (30.3)	16	16 (23.9)
Infection	8	4 (12.1)	20	16 (23.9)
Nausea	8	8 (24.2)	15	12 (17.9)
Cough	8	6 (18.2)	13	12 (17.9)
Edema	9	6 (18.2)	8	8 (11.9)
Weakness	4	4 (12.1)	13	11 (16.4)
Dehydration	5	3 (9.1)	11	8 (11.9)
Mucositis / stomatitis	1	1 (3.0)	14	12 (17.9)
Constipation	2	2 (6.1)	11	10 (14.9)
Vomiting	6	6 (18.2)	7	6 (9.0)
Neuropathy	3	3 (9.1)	9	7 (10.4)
Dizziness / lightheadedness	7	5 (15.2)	3	3 (4.5)
Hypokalemia	3	3 (9.1)	7	7 (10.4)
Taste alteration	4	2 (6.1)	6	6 (9.0)

Chapter 2. Statistical Analysis Plan

Initial Analysis Plan for Primary Outcome

Phase II data with single agent erlotinib in 216 subjects who had received ≥ 2 prior chemotherapy regimens demonstrated a RR of 10% (95% CI: 6-14%) (1). The study was designed as a two arm study from a clinical perspective, but the evaluated arm for the primary outcome of response rate was the combination arm. The erlotinib alone arm was included only so that we would be able to make comparisons in our correlative analysis between effects of erlotinib vs. effects of the combination of agents. The rationale for randomizing twice as many subjects to the erlotinib plus fulvestrant arm was that this was the only arm that was going to be evaluated for the primary endpoint. As an added benefit to this design, we felt that patients would be more inclined to participate if they were more likely to get an intervention (fulvestrant) that would be unavailable to them outside of the context of a clinical trial in the setting of metastatic lung cancer. Interestingly, the main incentive that drew many patients was an unanticipated one at the time of study initiation. Erlotinib costs approximately $100 per pill, and many patients were eager to have this medication provided at no cost as part of a clinical trial.

Based on these results, we sought to randomize 102 subjects in a 2:1 ratio to the fulvestrant plus erlotinib combination: erlotinib monotherapy arms, respectively. Randomization was 2:1 as carried out by a random permuted block design, with randomization using a Web-based system. Subjects were stratified based on gender and performance status (ECOG 0, 1 vs. 2). In a one-sided exact test, 68 subjects yielded a power of 82% (alpha= .10) to detect a 100% improvement in response rate with the combination of fulvestrant and erlotinib (expected RR=20%) compared to the historical data for erlotinib alone. The erlotinib monotherapy arm sought to recruit 34 subjects and served as a control arm for the subject population, but the study

was not powered to make formal statistical comparisons between the two arms.

A placebo was not included as part of the erlotinib arm based on practical considerations. We did not have a placebo for fulvestrant as part of our study agreement with AstraZeneca. In addition, it would have added costs to have a study pharmacist deliver fulvestrant vs. fulvestrant/placebo. In addition, there would have been ethical issues in an unnecessary intramuscular injection in these ill patients, many of whom were on anticoagulants for their oncologic condition. Of course, the lack of placebo does lead to the potential for bias. Radiology was unaware of the treatment assignment, but beyond lack of inclusion of this information in the requisition, radiologists were not formally blinded. As this was a multicenter study though, radiographic data was read by a large number of radiologists, and it is unlikely that any radiologist would feel so invested in the study as to bias their results in favor of either arm of the study.

Pitfalls of the Data Analysis Plan

We encountered several difficulties based on the duration of time that elapsed during the study. Interestingly, the study began as a trial of gefitinib and fulvestrant. However, development of gefitinib in the United States was halted after four subjects were enrolled on this trial. Data from those subjects is not included in this analysis as they did not receive the eventual study therapies that were assessed.

Further, a great deal was learned in the field from the time of study initiation until now. In particular, the role of EGFR mutations and the favorable association between these mutations and response to erlotinib was clarified during the conduct of the study. Since this study was designed in part to assess that relationship, the study did not include stratification by EGFR mutational status. Analysis by EGFR mutational status was planned as part of this study. In

retrospect, it may have been reasonable to stratify based on EGFR mutational status once the correlation between EGFR mutations and positive responses to erlotinib was known. However, that was difficult in part based on the fact that EGFR mutations was a study procedure that we had not intended to do in real time. If was not entirely practical to anticipate that subjects would wait for us to send the tissue to the University of Pittsburgh and have them analyze the tissue prior to enrollment on trial (which would have been needed if stratification was based on it).

Other issues that arose include that the "line of therapy" for which erlotinib was appropriate changed over the course of the study. Initially, an EGFR inhibitor was recommended after two lines of prior therapy. During the study, the guidelines shifted to include a recommendation for an EGFR inhibitor after one or more lines of therapy, and in EGFR mutant patients, the recommendation became that frontline therapy be erlotinib.[2] Therefore, as more known EGFR mutant patients enrolled after the recommendation for frontline therapy with EGFR inhibitors, there was a noted increase of EGFR mutant patients (and a resultant increase in response rate).

As a result, analysis by line of therapy is difficult, as it is highly dependent on date of enrollment and EGFR mutational status. Particularly at UCLA, where over a third of the subjects were enrolled, patients with known EGFR mutations were preferentially enrolled. We will perform logistic regression with the dependent variable of clinical benefit rate and linear regression analyses with the dependent variables of progression free survival and overall survival. Based on the tremendous importance of EGFR mutational status in these models, analysis by regression will be limited to subjects for which EGFR mutational status is known. All models will include EGFR mutational status so that any additional variable that are independently predictive of outcome can be identified.

In addition, we now recognize the 8% response rate in EGFR wildtype patients with erlotinib seen in this study is unusual and encouraging. In a "between arm" comparison, it is not statistically different, however, when compared to historical controls it is very different (generally a response rate of < 1% would be expected in this setting)[3]. Assessments were made based on clinical benefit rate, although that was not a pre-specified outcome.

We did not include a formal plan for dropouts either after the time of randomization or after the time of therapy initiation, which turned out to be an error. We attempted to add additional four patients to reach 102 subjects treated, but in the end, 6 subjects received no treatment, so only 100 subjects were randomized. Further 23 subjects were not able to be assessed for the primary endpoint (response rate).

Modified Analysis Plan for the Primary Outcome:

Based on the initial data analysis plan, we met our primary endpoint of a response rate above 20%. However, based on thing that have been mentioned above, the relevance of this finding is unclear. Therefore, the primary endpoint of the trial was changed from the primary endpoint as compared to historical controls in the original grant. The study primary endpoint was to determine the objective response rate (RR) as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.0) in erlotinib and erlotinib plus fulvestrant treatment arms. Median PFS and OS were estimated from Kaplan-Meier curves. Stratified log-rank test was used to test the difference in PFS and OS between treatment arms.

Statistical Analysis of Tissue Biomarkers

EGFR mutational status was evaluated by the Stabile Group in Pittsburgh using pre-treatment tissue samples. However, if a subject had EGFR mutational analysis in another CLIA certified laboratory, we did not require that the test be repeated. Evaluation of tissue biomarkers,

particularly ER-β, is being analyzed by Dr. Press at USC to help determine the relationship between ER-β levels and clinical outcomes. For ER-β staining, ROC curves will be obtained, and area under the curve analyses will be conducted evaluating percentage staining as compared to RR, PFS and OS. We will identify the Youden Index for each outcome to identify the point that we consider to be predictive of response to fulvestrant plus erlotinib in the arm receiving both therapies. We will also evaluate the ROC curves for the biomarker in the erlotinib alone arm to ensure that the biomarker is not merely prognostic, but is instead predictive of a superior outcome with therapy directed against ER.

Safety Analyses

All randomized and treated patients were included in the safety analysis. In general, the safety analysis was descriptive in nature and was based on Genentech and AstraZeneca standards. No hypothesis testing was planned prospectively.

The JCCC Data Safety Monitoring Board (DSMB) constituted prior to the treatment of the first patient. The role of the DSMB was to review the study from a safety perspective and to make recommendations regarding the continuation of the trial. The DSMB met twice yearly to review the incidence and severity of all AEs and SAEs. Prior to each meeting, members of the DSMB were provided with all relevant data, according to the statistical analysis plan of the study. In the event of unanticipated severe AEs or SAEs, the DSMB convened immediately to review the event(s) and ensure the safety of patients on the trial. After each meeting, the DSMB issued one of three recommendations: (1) continue with the trial as planned, (2) continue with the trial, with modifications to the protocol or (3) discontinue the trial due to serious safety concerns.

Interim Analysis

Two interim analyses occurred: (1) after 5 patients were treated with the combination to

ensure that there was no safety problem (as the only phase I data available was with the combination of a similar combination gefitinib and fulvestrant) and (2) after half of the patients had had their 8-week assessment. If the response rate in this subset of patients had been ≤ 5% (50% of the expected historical response rate of 10%), the trial would have been terminated for futility. Safety was analyzed at the interim analysis and on a biannually basis to assess AEs and SAEs. Monthly conferences were held to discuss the safety status of subjects in this protocol. In addition, the DSMB evaluated safety reports on a quarterly basis.

Response Evaluation Criteria in Solid Tumors (RECIST 1.0)[4]

Eligibility

1. Only patients with measurable disease at baseline were included since objective tumor response was the primary endpoint.
    a. Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology or lesions that can be accurately measured in at least one dimension with longest diameter >20 mm using conventional techniques or >10 mm with spiral CT scan.
    b. Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.
2. All measurements were taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations were performed as closely as possible to the beginning of

treatment and never more than 4 weeks before the beginning of the treatment.

3. The same method of assessment and the same technique were used to characterize each identified and reported lesion at baseline and during follow-up.
4. Clinical lesions were considered measurable when they were superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, was recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI were performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT was performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) was not used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy 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 centers. Therefore, the utilization of such techniques for objective tumor response should be

restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone were not used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, identified as target lesions and recorded and measured at baseline.
- Target lesions were selected on the basis of their size (lesions with longest diameter) and their suitability for accurate repeated measurements (by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions was calculated and reported as the baseline sum LD. The baseline sum LD referenced to characterize objective tumor.
- All other lesions (or sites of disease) was identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each was noted throughout follow-up.

Response Criteria

- Evaluation of target lesion
    - **Complete Response (CR)**: Disappearance of all target lesions
    - **Partial Response (PR)**: At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
    - **Progressive Disease (PD)**: At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

- **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

- Evaluation of non-target lesions
  - **Complete Response (CR)**: Disappearance of all non-target lesions and normalization of tumor marker level
  - **Incomplete Response/Stable Disease (SD)**: Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
  - **Progressive Disease (PD)**: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Evaluation of Best Overall Response

- The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment depended on the achievement of both measurement and confirmation criteria

Target lesions	Non-target lesions	Evaluation of non-target lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time were classified as having “symptomatic deterioration”. Every effort should be made to document the objective

progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it was recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. When confirmation of response is not feasible, it was made clear when reporting the outcome of such studies that the responses were not confirmed.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD was measured from the start of the treatment until the criteria for disease progression are met, referring to the smallest measurements recorded since the treatment started.

Reporting of results

- All patients included in the study are assessed for response to treatment. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

References

1. Hidalgo M, Siu L, Nemunaitis J, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 2001;19:3267-79.

2. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011; 29: 2866–74.

3. Laurie SA, Goss GD. Role of epidermal growth factor receptor inhibitors in epidermal growth factor receptor wild-type non–small-cell lung cancer. J Clin Oncol *2013;*31*:*1061–1069.

4. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-216.