# Gefitinib (Iressa) in Non-Small Cell Lung Cancer: A Retrospective Analysis

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## Abstract

**Background** This study is a retrospective review of 50 non-small cell lung cancer (NSCLC) patients who received 250 mg/day gefitinib (Iressa) as third-line monotherapy.

**Patients and Methods** 50 patients were included in this study. The data were collected from five tertiary care centers in Lebanon.

**Results** The mean age of patients was 61 (median 64); 72% were male and 28% female. All 50 patients received 250 mg oral gefitinib as monotherapy for a mean duration of 3.9 months (range 1-19 months). One-year and three-year survival was 73% and 21% respectively. Patients with Eastern Cooperative Oncology Group (ECOG) status 0-1 as compared to patients with ECOG status 2-4 enjoyed significantly better survival and response rates.

**Conclusion** From the data it appears that patients may benefit from earlier administration of gefitinib.

## Introduction

Lung cancer is the leading cause of cancer-related mortality in the world accounting for 32% of all cancer-related deaths among males and 25% among females and accounts for 13% of all cancers in males and 12% in females [1]. In Lebanon, the incidence of lung cancer in males is 14.1%, but is only 4.3% among women [2]. Despite advances in diagnostic and therapeutic interventions, the prognosis of patients with advanced stage non-small cell lung cancer (NSCLC) remains dismal [3]. For patients who fail to respond to first-line therapy, response rates to second-line therapeutics range from 7 to 27% [4]. Currently, there is no approved treatment for patients who fail 2 different chemotherapy regimens.

The current standard of care for patients diagnosed with advanced lung cancer is 4-6 cycles of platinum-based chemotherapy. From the evidence it appears that platinum-based chemotherapy offers a 2-month survival advantage compared to best supportive care alone. Because treatment for advanced lung cancer is only palliative, clinicians must weigh any possible survival advantage, symptom control and quality of life improvements against the toxicities of chemotherapy. Treatments with targeted agents such as gefitinib are considerably less toxic than systemic chemotherapies.

Gefitinib (Iressa) is an epidermal growth factor receptor inhibitor belonging to the anilinoquinazoline class of compounds [5]. Epidermal growth factor receptor (EGFR) is a transmembrane receptor identified as the cellular homologue of the viral oncogene v-erb. Many solid tumors of epithelial origin over-express EGFR and overexpression is associated with poor prognosis. Therefore, EGFR inhibition is a rational anticancer strategy.

Preliminary studies with gefitinib on human tumor xenografts in experimental mice showed a dose-dependent inhibition of growth of different tumors including breast, lung and prostate. Tumor growth was completely inhibited at doses above 200 mg/kg/d. Although the inhibition was sustained for the duration of the treatment, tumor growth resumed with treatment cessation [5].

Data from phase II studies of third-line gefitinib indicate that about 43% of patients experience symptom improvement and 12% have a radiographic partial response. In one study, one-year survival was 25% [4]. Unfortunately, phase III studies of concurrent treatment with carboplatin-paclitaxel plus gefitinib failed to support the survival trends noted in phase II gefitinib monotherapy trials [6-8].

## Survey Data

Patient data was obtained from treating oncologists in 5 tertiary care centers and included smoking history, pathology, treatment and follow-up.

### *Statistical analysis*

Comparison of continuous variables between various sub-groups was performed using a two-tailed t-test. The relationship between continuous and non continuous variables was evaluated using a Spearman correlation coefficient. Chi-square analysis was used to compare discrete variables between various sub-groups. The

analyses were performed using SPSS software version 13.0 (SPSS, Chicago, Illinois). Statistical significance was set at $p<0.05$.

## Patients

Patients were treated until disease progression. The clinical characteristics of all patients are shown in *Table 1*. The mean age of patients was 61 years (median 64); 72% were male and 28% female. 78% of patients had received platinum-based chemotherapy and 92% had received non-platinum chemotherapy. 41% of the patients had received first-line chemotherapy prior to starting gefitinib, 41% had received second-line chemotherapy and 18% had received third-line treatment. Radiation therapy was administered to 54% of the patients, while 24% had prior surgery. As for histological type, 44.1% had adenocarcinoma, 35.3% had squamous cell carcinoma, 5.9%, 8.8% and 5.9% had non-small cell lung carcinoma, large cell, and epidermoid types respectively.

## Results

Overall response rate to gefitinib was 12%; 2 patients (4%) had a complete response and 4 (8%) had a partial response. Data was missing on 3 patients with overall clinical benefit and disease control in 36%. 24% of the patients had stable disease, while 58% exhibited continued disease progression. When stratified by histology type, 14 patients had adenocarcinoma *(Figure 1)*. Of those 1 had a complete response, 2 had stable disease and 11 had progressive disease while on gefitinib. Of the 11 patients who had a squamous cell carcinoma, 2 had partial response, 2 had stable disease and 7 had progressive disease. 7 patients had other histological subtypes, 2 had partial response and 2 had stable disease, with progressive disease in 3 patients. It is worth noting that the only patient with complete response and histology data available had adenocarcinoma subtype. Female patients tended to have poorer prognosis as 11 out of 13 (84.6%) had progressive disease on gefitinib versus 18 out of 34 males (52.9%), however the difference was not significant ($p=0.91$).

Of the 25 patients who had Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores 0-1, 11 (44%) had disease progression versus 12 of the 15 patients (80%) who had ECOG performance status of 2 or more. ($p = 0.046$). Survival at 1 year was 73%, and 21% at 3 years. Patients with ECOG PS 0 or 1 had a 31% chance of 3-year survival whereas ECOG PS 2 and 3 was associated with a 3-year survival probability of 17%. Mean survival was 40 and 20 months for the ECOG subgroups respectively ($p= 0.044$) *(Figure 2)*. No grade 3 to 4 toxicities were observed.

## Discussion

Gefitinib is an oral agent that inhibits EGFR tyrosine kinase, resulting in antitumor activity among patients with previously treated NSCLC [9]. This retrospective analysis of 50 Lebanese patients with NSCLC who did not respond to prior treatment and were treated with oral gefitinib (<Iressa>, ZD1839; AstraZeneca) 250 mg/day. Although the response rate to gefitinib is rather low, in the order of 12%, the drug can induce full remission in a selected subset of patients. Two patients out of fifty (4%) in the present analysis experienced disease remission.

Data obtained in this analysis is comparable with published data from the phase II IDEAL 1 and 2 studies [10, 11]. In these studies, administration of second or third-line gefitinib provided disease control in 42–54% of patients with advanced or metastatic NSCLC who were previously treated with platinum-based chemotherapy. Overall survival was 35% and 25% in IDEAL 1 and 2 respectively. In our study, disease control was experienced by 36% of patients (4% had CR, 8% had PR, and 24% had SD). One-year and three-year survival was 73% and 21% respectively.

Although large-scale phase III trials such as INTACT 1 and 2 failed to show any benefit from the addition of gefitinib to standard chemotherapy regimens, the disappointing result might be attributed to inadequate patient selection. Subsequent to publication of INTACT 1 and 2, an EGFR mutation which confers sensitivity to gefitinib was identified in 2004 [12]. In addition, multiple studies have confirmed that patients most likely to respond to gefitinib are never-smoking females of Asian ethnicity with adenocarcinoma or bronchioalveloar histology [5]. In the present analysis, patients were selected for third-line gefitinib treatment based solely on failure of previous trials of chemotherapy rather than demographic or disease characteristics now known to be associated with superior response. In addition, it should be noted that gefitinib can provide durable disease remissions to patients who do not have any established characteristics of response.

Recently, a placebo-controlled phase III study (the ISEL study) investigated the effect of gefitinib on survival [13]. At a median follow-up of 7.2 months, median survival did not differ significantly between groups in the overall population. However, subgroup analyses showed significantly longer survival for never-smokers and those of Asian origin who received gefitinib compared to placebo. Never smokers had a median survival of 8.9 vs 6.1 months ($p=0.012$). Asians had a median survival 9.5 vs 5.5 months $p=0.01$).

In addition, our analysis confirmed that patients with a lower ECOG PS (0-1) have better response rates and better survival. This implies that gefitinib treatment may be more effective if initiated early. However, because gefitinib is associated with considerably less toxicity than traditional chemotherapies, it is worth considering as a treatment option for poor PS patients as well.

## Conclusion

Gefitinib has been approved by the Food and Drug Administration (FDA) as the first molecularly targeted monotherapy for patients who are refractory to both platinum-based and docetaxel chemotherapies [10, 11].

Our data indicates that the response rate to gefitinib is better for patients with good PS, so starting it earlier for a selected subset of patients may produce better response rates and survival. Additional studies on selection of target populations for gefitinib are warranted.

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## TABLES

Table 1. Main characteristics of the patients

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|---|---|
| Age | 61 ± 9.9 |
| Mean Duration of Iressa Rx | 3.9 ± 3.6 |
| Gender | 72% male, 28% female |
| Prior Surgery | 24% Yes, 74% No, 2% Missing |
| Prior Radiation | 54% Yes, 26% No, 20% Missing |
| ECOG Status | 0 8%, 1 44%, 2 28%, 3 4%, Missing 16% |
| Staging (stage-%) | IIB-6%, IIIA-14%, IIIB-18%, IV-48%, Missing-14% |
| Cisplatin Containing Chemo-Rx | 70% Yes, 20% No, 10% Missing |

Rx: therapy

## FIGURES

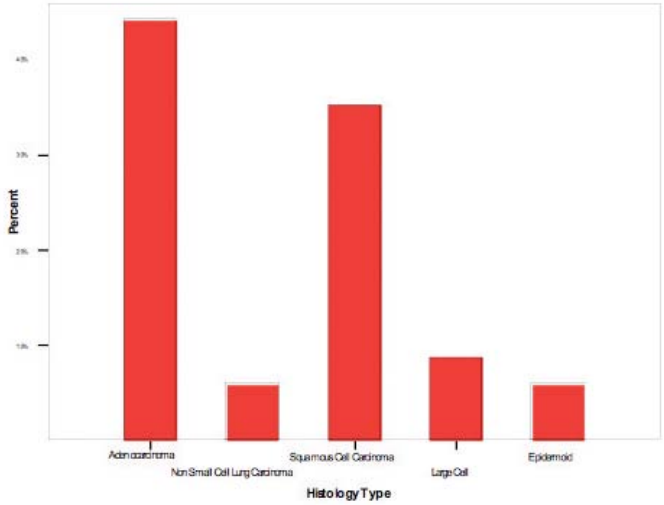


Figure 1. Cases stratified by Histological type

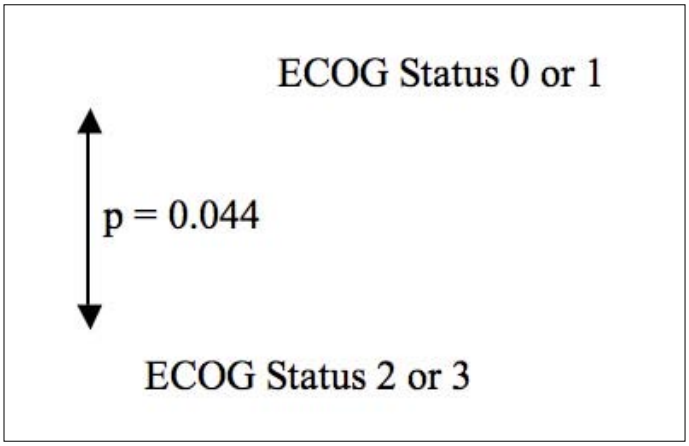


Figure 2. Survival Stratified by ECOG Performance Status