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with previously treated  
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## Gefitinib (ZD1839) in Previously Treated Advanced Non-Small-Cell Lung Cancer: Experience From a Single Institution

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**Background:** We conducted an analysis of gefitinib in patients with advanced non-small-cell lung cancer (NSCLC) to assess the antitumor efficacy of this epidermal growth factor receptor tyrosine kinase inhibitor.

**Methods:** Our single-center, prospective landmark analysis included 183 patients with advanced NSCLC who received 250 mg of gefitinib orally once daily in an expanded-use program at our institution. Thirty-three of the 183 patients were previously untreated. The patients included in this analysis had all received at least 12 weeks of gefitinib.

**Results:** The objective tumor response rate was 3.8%, but an additional 53.5% of patients experienced clinically meaningful disease stabilization. Median progression-free survival time was 3.6 months, and median overall survival time was 8.8 months. The 1-year survival rate for the entire cohort was 35%. Predictors of longer survival included female gender, adenocarcinoma or bronchoalveolar carcinoma histology, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Adverse events were generally mild (grade 1 or 2) and consisted mainly of skin reactions and diarrhea.

**Conclusions:** In this single-center experience, gefitinib demonstrated clinically significant antitumor activity and provided good palliation in a predominantly pretreated group of patients. Our results, which are likely to be reproducible in a community setting, demonstrated a 1-year survival rate of 35% in a cohort of patients who were able to take the drug for at least 12 weeks.

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## Introduction

The epidermal growth factor receptor (EGFR) belongs to a subfamily of four closely related receptors: EGFR (ErbB-1), HER2/*neu* (ErbB-2), HER3 (ErbB-3), and HER4 (ErbB-4). The EGFR is a 170-kd plasma membrane glycoprotein composed of an extracellular ligand-binding domain, a transmembrane lipophilic segment, and an intracellular protein (tyrosine) kinase (TK) domain with a regulatory carboxyl terminal segment.<sup>1,2</sup> The receptors exist as inactive monomers that homo- or hetero-dimerize (between EGFR and another member of the Erb receptor family) after ligand activation.<sup>1,2</sup> The EGFR can also be activated by ligand-independent mechanisms.<sup>2</sup> Activation of the EGFR TK has been identified as a key initiating event that generates a cascade of intracellular signaling events regulating cell proliferation, differentiation, survival, angiogenesis, and metastasis, all processes that are crucial to cancer progression.<sup>3</sup>

EGFR is expressed, overexpressed, or dysregulated in many human solid tumors, including breast, ovarian, non-small-cell lung cancer (NSCLC), colorectal, and head and neck cancers.<sup>4,5</sup> Its activation in these tumors seems to promote tumor growth by increasing cell proliferation, motility, adhesion, and invasive capacity<sup>6</sup> and by blocking apoptosis.<sup>7</sup> In support of its important role in tumor biology, EGFR overexpression and dysregulation have been reported to be associated with indices of poorer prognosis in patients and are associated with metastasis, late-stage disease, and resistance to chemotherapy, hormonal therapy, and radiotherapy.<sup>5,8,9</sup>

Given the importance of EGFR in epithelial tumor biology, several EGFR-targeted cancer therapies are currently under development. Gefitinib (ZD1839) is an orally active, selective EGFR-tyrosine kinase inhibitor (TKI) that inhibits EGF-stimulated EGFR autophosphorylation in cell lines at submicromolar concentrations (50% inhibitory concentration range, 0.02 to 0.08  $\mu\text{mol/L}$ ).<sup>10</sup> In preclinical studies, gefitinib demonstrated antitumor activity against EGFR, expressing NSCLC, ovarian, breast, and colon cancer cell lines<sup>11,12</sup> and xenograft models.<sup>10</sup>

Preclinical toxicology studies showed that gefitinib had a favorable toxicity profile over 6 months of oral dosing in animals, with mechanism-based, dose-dependent reversible effects on the skin, cornea, kidney, liver, and ovaries.<sup>10</sup> This toxicity profile is predictable since EGFR signal transduction is involved in the normal physiology of these organs. Gefitinib pharmacokinetics in preclinical models demonstrated its good oral bioavailability and predicted its use as a daily

oral treatment in humans. Two placebo-controlled studies investigated the pharmacokinetics and tolerability of single oral doses of gefitinib (1 to 75 mg) and multiple doses of gefitinib (100 mg once daily for 3 days).<sup>13</sup> Gefitinib was well tolerated at doses up to 100 mg/day, with a low incidence of mild, transient adverse events. These studies also demonstrated that gefitinib is orally bioavailable in humans — after a single oral dose of 250 mg, the mean absolute bioavailability of ZD1839 was 57% (90% confidence interval, 49% to 68%) — and is absorbed moderately slowly, with the maximal plasma concentration ( $C_{\text{max}}$ ) attained between 3 and 7 hours after administration.<sup>10</sup> The elimination half-life of 28 hours suggests that once-daily oral administration is appropriate.<sup>13</sup> Binding of gefitinib to plasma proteins was approximately 90% and was independent of the gefitinib plasma concentration. Furthermore, absorption of gefitinib was not significantly affected by concomitant food intake.<sup>10</sup>

In an open-label, phase I, dose-escalation safety/tolerability trial of oral ZD1839 (150 to 1,000 mg/day) administered once daily for 28-continuous-day cycles until disease progression or undue toxicity, rash and diarrhea were found to be the dose-limiting toxicities at an 800 mg/day dose level but were generally mild at 600 mg/day or less.<sup>14</sup> Frequent treatment-related grade 1/2 adverse events were diarrhea (55%), asthenia (44%), and acne-like follicular rash (46%). Pharmacokinetic analysis showed that steady state occurred by day 7 and confirmed the suitability of once-daily oral dosing. Two other phase I studies confirmed these findings.<sup>3,14-16</sup> Responses were seen across the dose range from 150 to 800 mg/day. However, the majority of dose interruptions and reductions due to toxicity occurred in patients receiving more than 600 mg/day. Hence for phase II and phase III studies, two doses levels were selected. The dose level of 250 mg was selected because it was higher than the lowest dose level at which objective responses were seen, while 500 mg/day was the highest dose level that was well tolerated over an extended period of time. A recently reported randomized phase II trial comparing the efficacy of the 250 mg/day dose level vs. the 500 mg/day dose level confirmed that the efficacy was similar for the two dose levels, with toxicities seen more frequently at the higher dose level.<sup>17</sup>

We report here a prospective, landmark analysis of a single, tertiary cancer center experience of patients with advanced NSCLC treated with gefitinib on an expanded use program given orally daily at a dose of 250 mg. Since patients were enrolled on an expanded-use program, no patient was refused drug and a significant proportion of patients died before an adequate trial of the drug was possible. Hence, we chose to

report a landmark analysis, thus restricting the evaluation to patients who had received the drug for at least 3 months. This selection process ensured that the patients had received an adequate trial of the drug.

## Patients and Methods

### Study Design

The enrolled patients were on an open-label, expanded-use program available at our institute. All gave informed consent and signed an informed consent approved by the University of South Florida Institutional Review Board. The primary objective was to evaluate overall survival (OS). Secondary objectives were to estimate progression-free survival (PFS), response rate, and stable disease rates.

### Patient Eligibility

Patients with histologically or cytologically confirmed advanced NSCLC with metastatic or recurrent disease not curable with surgery or radiotherapy at study entry were allowed to enroll. They could have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, 2, or 3. Patients with stable brain metastases were eligible, but those receiving palliative radiation therapy had to complete radiation before they were allowed to enroll. Patients were con-

sidered for inclusion in this landmark analysis only if they survived till the 12-week efficacy evaluation visit.

### Treatment

Patients received gefitinib at 250 mg orally once daily. Treatment was continued uninterrupted until disease progression, death, or withdrawal of consent. Gefitinib treatment could be interrupted for a maximum of 14 days. No other systemic anticancer treatment was allowed during the trial, but use of palliative radiotherapy for isolated bone metastases was permitted. Baseline assessments were performed within 2 weeks before study entry. After the start of treatment, patients were assessed for toxicity after the first 4 weeks of treatment. For efficacy, patients were evaluated every 12 weeks.

A 14-day dose interruption was allowed for resolution of possible gefitinib toxicity. Specifically for diarrhea, this 14-day holiday allowed resolution of diarrhea as well as correction of hydration and use of antimotility agents. With appropriate supportive care (antimotility agents for diarrhea and topical dermatological or systemic antibiotics for skin rash), gefitinib could be restarted at the same dose.

### Statistical Consideration

Objective response rates (complete response, partial response, stable disease, or progressive disease) were assessed according to the Southwest Oncology Group modification of WHO criteria. For the analyses of OS and PFS, measurement started on the day treatment with gefitinib began. For OS, the cut-off was

Table 1. — Patient Characteristics (n = 183)

Age (yrs):	
Range	35-94
Median	68
Gender:	No. of Patients
Male	103
Female	80
Performance status (ECOG):	
0	58
1	78
2	32
3	14
Missing	1
Histology:	
Adenocarcinoma	81
Bronchoalveolar carcinoma	19
Squamous-cell carcinoma	33
Large-cell carcinoma	6
NSCLC (not otherwise specified)	43
Carcinoid	1
Number of prior chemotherapy regimens:	
0	33
1	74
2	48
3	21
4	5
5	2

Table 2. — Progression-Free Survival (PFS) and Overall Survival (OS) in Different Subgroups

	PFS (months)	P Value	OS (months)	P Value
Entire group (n = 183)	3.6	NA	8.8	NA
Age (years):				
≤68	3.2	.19	8.0	.28
>68	4.4		10.4	
Gender:				
Male	3.3	.13	8.3	.05
Female	4.0		11.2	
Histology:				
Adenocarcinoma	6.5	.03	11.2	.04
Bronchoalveolar carcinoma	5.2		10.6	
Squamous-cell carcinoma	3.8		7.6	
Large-cell carcinoma	2.8		4.2	
NSCLC (not otherwise specified)	3.3		8.0	
Performance status (ECOG):				
0-1	4.7	.02	9.6	.001
2-3	2.8		5.6	
NA = not applicable				

either on the date of death or on the date last seen alive. For PFS, the patient's time ended at disease progression or death. For those not experiencing either endpoint, the patient's time ended when the patient was last seen alive and free from progression.

All OS and PFS probability estimates were based on the Kaplan-Meier method<sup>18</sup> with standard errors based on the Greenwood formula.<sup>19</sup> Comparisons of groups with respect to OS and PFS were based on the log rank test and *P* values were two-sided.

Toxicity data were captured only if they were classified as serious adverse events (SAEs). An SAE was an adverse event occurring while on treatment with gefitinib or within 30 days after discontinuation of gefitinib and was associated with death, a life-threatening event, persistent or significant disability/incapacity, or inpatient hospitalization. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.<sup>20</sup>

## Results

Of the entire cohort of 395 patients who were treated with gefitinib, 211 were evaluated at the 4-week toxicity evaluation visit. One hundred eighty-three patients were eligible for inclusion in this landmark analysis of patients who presented for the first

12-week efficacy evaluation visit. Thirty-three of the 183 patients had received no previous systemic therapy for lung cancer. All of the previously untreated patients enrolled on this trial either had ECOG PS 2 or 3 (18 patients) or had adenocarcinoma or bronchoalveolar carcinoma (BAC) (15 patients). Patient characteristics are summarized in Table 1. The median age for the entire cohort was 68 years (range 35 to 94 years), and women comprised 44% of the study population. Seventy-four percent had an ECOG PS of 0 or 1, and 55% had either adenocarcinoma or BAC. Gefitinib was given as first-line treatment in 18% of patients, second-line treatment in 40%, and third-line treatment in 26%. Hence, not surprisingly, this cohort of patients had several favorable prognostic characteristics that enabled them to be alive at the 12-week efficacy evaluation visit.

The overall objective response rate was 3.8%. Two patients achieved complete responses and 5 patients had partial responses. An additional 53.5% of patients had stable disease, giving a response plus disease stabilization rate of 57.3%.

Data for OS and PFS are summarized in Table 2. Estimated PFS was 18% (standard error [SE] = ±3%) at 1 year, with a median of 3.6 months (Fig 1A). Estimated OS was 35% (SE = ±5%) at 1 year and the median OS time was 8.8 months (Fig 1B). There were no statistically significant differences in PFS or OS in elderly

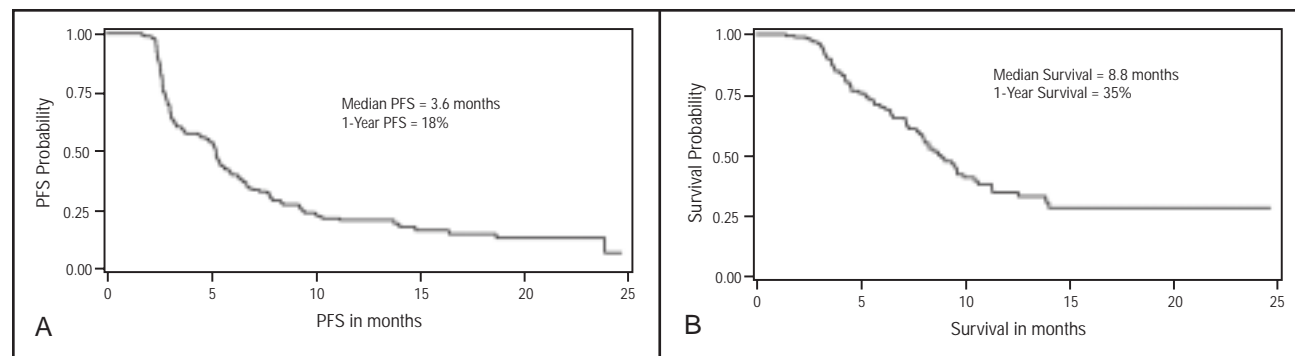


Fig 1. — Progression-free survival (A) and overall survival (B) for all patients.

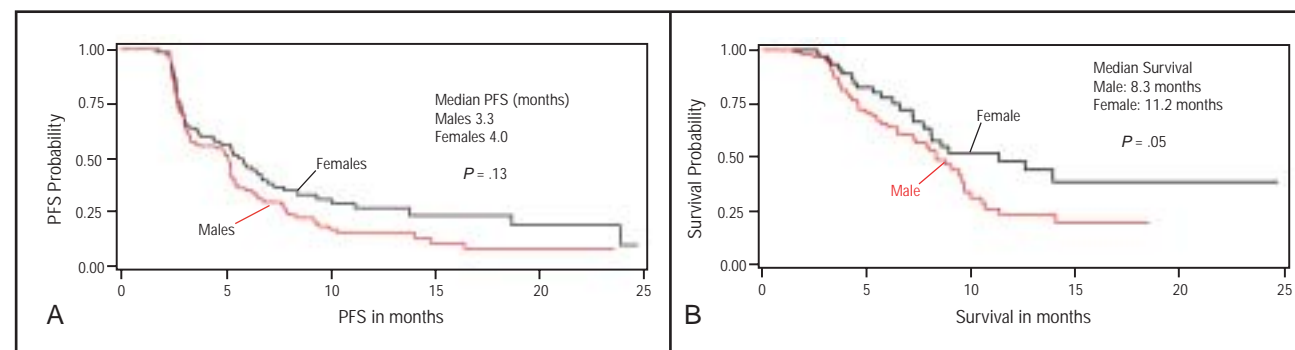


Fig 2. — Progression-free survival (A) and overall survival (B) stratified by gender.

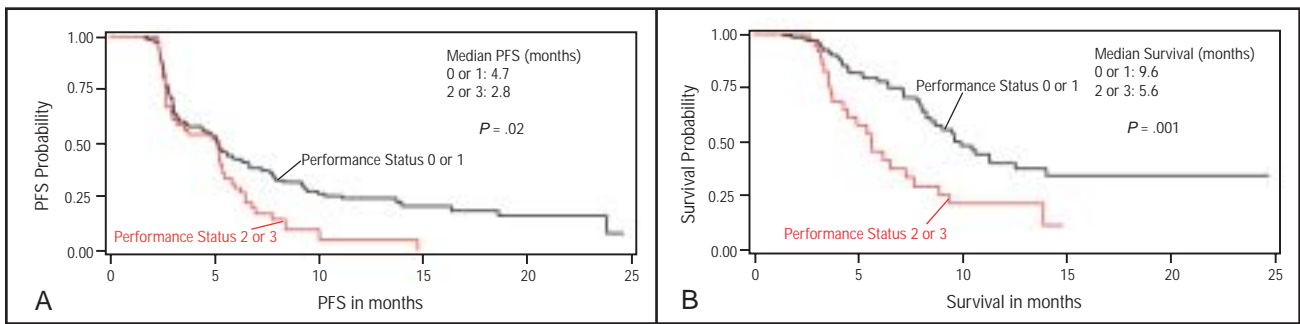


Fig 3. — Progression-free survival (A) and overall survival (B) stratified by performance status.

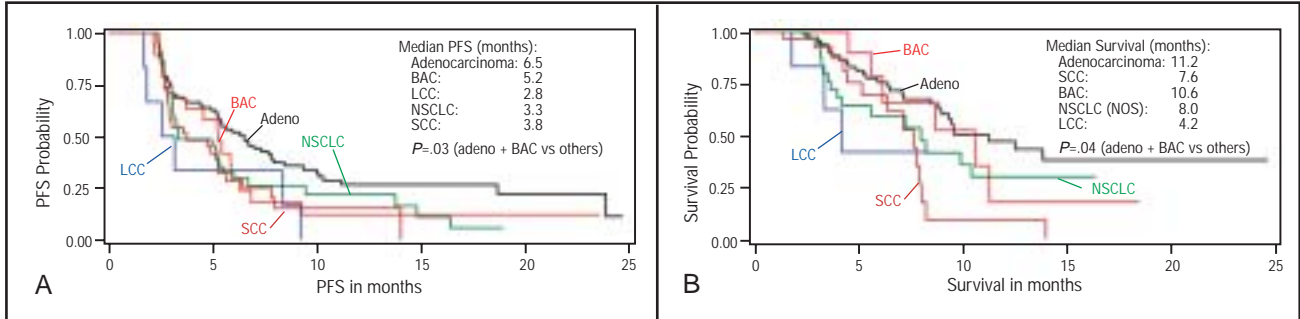


Fig 4. — Progression-free survival (A) and overall survival (B) stratified by tissue type (LCC = large-cell carcinoma, BAC = bronchoalveolar carcinoma, NSCLC = non-small-cell lung cancer, SCC = squamous-cell carcinoma).

patients (age >68 years) compared with younger patients. We saw no significant difference ( $P=.13$ ) between men and women for PFS, but women did significantly better ( $P=.05$ ) with respect to OS (Figs 2A-B). Predictably, patients with a PS of 0 or 1 had a statistically significant better PFS and OS compared with patients with a PS of 2 or 3 (Figs 3A-B). Stratification by tumor type indicated that there were statistically significant differences in PFS and OS ( $P=.03$  and  $.04$ , respectively) when adenocarcinomas plus BAC were compared with the rest of the histologies (Figs 4A-B).

We also explored the link between the duration of time from initial diagnosis of metastatic or recurrent disease to starting gefitinib vs duration of time that the patient stayed on gefitinib. We found a linear correlation, the slope of which was statistically significant,

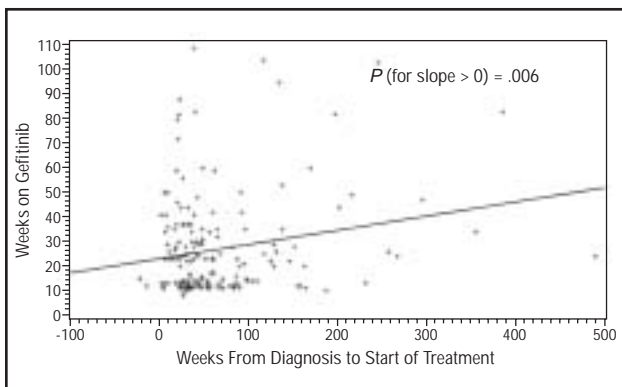


Fig 5. — Plot of weeks on gefitinib vs time to start rx.

thereby suggesting that time to progression on gefitinib may be at least partially a function of the indolent biology of some tumors (Fig 5).

Toxicities were generally mild in this cohort of patients, with diarrhea and rash being the most commonly observed side effects. The most common SAE-associated grade 3 or 4 toxicity was dyspnea, which occurred in 7 patients (3.8%). However, in all cases, investigators attributed the dyspnea to non-drug-related causes. Fatigue was the second most common SAE. It occurred in 5 patients, but in 4 of these was determined to be disease-related. Other SAE-associated events included bone pain, nausea, and one instance of grade 4 hemoptysis that was determined to be caused by progressive disease.

## Discussion

We report here the single-center experience of patients receiving gefitinib on an expanded-use program. To be eligible for this landmark analysis, patient had to have taken gefitinib for 12 weeks. The experience of the entire group will be reported separately.

Patients had to meet only a few essential eligibility criteria for enrollment in the expanded-use program. This makes our data reproducible and applicable to patients seen in a community setting and therefore especially relevant. Nevertheless, our data are similar

to the more rigorously conducted but uncontrolled IDEAL 1 trial (Iressa Dose Evaluation in Advanced Lung Cancer). IDEAL 1 is a recently reported multicenter, randomized, double-blind but not placebo-controlled trial of two dose levels of gefitinib (250 vs 500 mg/day).<sup>17</sup> However, two critical differences exist between the IDEAL 1 trial and this report: (1) the IDEAL 1 investigators included all patients in their analyses, whereas our report is an analysis of patients who received gefitinib for at least 12 weeks, and (2) 18% percent of our patients were previously untreated, whereas all patients in the IDEAL 1 trial received gefitinib as either second-line or third-line treatment. Response rates were 10.4% in the IDEAL 1 trial (for non-Japanese patients) vs 3.8% in our trial, disease stabilization occurred in 35.9% vs 53.5%, PFS was 2.7 months vs 3.6 months, median survival was 7.6 months vs 8.8 months, and 1-yr survival was 35% vs 35% for the 250 mg/day arm of the IDEAL 1 trial and our trial, respectively. Additionally, in our trial, female patients and adenocarcinoma (including BAC) histology had statistically significantly improved survival. The IDEAL 1 trial was in concordance, with multivariate analyses showing the backward regression model showing that female gender and histology were two of the three factors that retained significance at the 5% level. Prior immunotherapy or hormonal therapy was the third factor.

It is unknown why the adenocarcinoma histology was associated with better survival than squamous-cell carcinoma, especially since the latter expresses EGFR more commonly. The IDEAL I investigators suggest that compared with other histologies, the adenocarcinomas may have a more indolent course.<sup>17</sup> Johnson and Arteaga<sup>21</sup> suggest that the relative sensitivity of adenocarcinomas to gefitinib may be secondary to higher coexpression of HER2 (36% for adenocarcinomas vs 1% for squamous-cell carcinomas),<sup>22</sup> allowing for not only the inhibition of EGFR-EGFR homodimers but also EGFR-HER2 heterodimers accounting for the relative sensitivity of adenocarcinomas to gefitinib. Several authors have suggested that overexpression of HER2 has negative prognostic implications and predicts for chemotherapy resistance.<sup>23</sup> Additionally, gefitinib has been shown to be active in HER2-overexpressing tumors.<sup>24,25</sup>

Age was not of prognostic significance; elderly patients fared as well as their younger counterparts. This is in agreement with several recently reported randomized trials.<sup>26,27</sup> Predictably, however, patients with better performance status (0 or 1) had significantly superior PFS and OS (Figs 3A-B).

To evaluate whether the response to gefitinib or disease stabilization with gefitinib may be more of a

function of indolent tumor biology, we studied the duration that the patient had the disease prior to initiation of gefitinib vs the duration that they stayed on gefitinib once treatment began. There was a statistically significant correlation between the two parameters: the longer the duration of diagnosis before initiation of treatment with gefitinib, the longer patients remained on therapy without progression (Fig 5). This leads us to speculate that tumors with an intrinsically slow tumor biology tend to be more dependent on the EGFR pathway and therefore more susceptible to gefitinib therapy. Put another way, EGFR-dependent tumors may be more indolent than EGFR-independent tumors. Perhaps, in the more aggressive tumors, the EGFR blockade may be bypassed by redundancy in the signaling pathways or by accumulation of additional mutations accounting for its rapid progression. Hence, EGFR overexpression may be an early event in lung carcinogenesis, and early EGFR overexpression has been demonstrated in the bronchial epithelium of high-risk smokers.<sup>22</sup> It is present at the stage of basal cell hyperplasia and persists through squamous metaplasia, dysplasia, and carcinoma in situ. However, one could speculate that the tumor does not remain EGFR-dependent for long and eventually becomes EGFR-independent and possibly consequently more aggressive.

Another frequently debated question is whether EGFR overexpression is necessary for gefitinib response. Recent evidence suggests that gefitinib response occurs across a wide range of EGFR expression levels.<sup>28,30</sup> In cell lines, overexpression of other factors may predict for resistance to gefitinib. Overexpression of the antiapoptotic protein Bcl-2 decreased the response to gefitinib treatment.<sup>30</sup> Evaluation of the mitogen-activated protein kinase/extracellular signal-regulated kinase and phosphatidylinositol 3'-kinase/Akt pathways showed considerable inhibition of these pathways by gefitinib in the highly sensitive control A431 cells (a vulval squamous-cell carcinoma cell line), whereas one or both of these pathways remained active upon anti-EGFR treatment in NSCLC cell lines (NCI-H460, NCI-A431 and A549). In addition, treatment with specific inhibitors of mitogen-activated protein kinase or phosphatidylinositol 3'-kinase resulted in a smaller effect on proliferation than simultaneous treatment with both inhibitors, whereas induction of apoptosis was observed only when both pathways were blocked.<sup>30</sup> Together, these data suggest that persistent activity of either of these signaling pathways is involved in the lack of sensitivity of NSCLC cell lines to EGFR inhibitors.<sup>30</sup> Hence, a better understanding of the effect of gefitinib on the downstream signaling of the human epidermal growth factor pathways will shed further light on the mechanisms of resistance to gefitinib, which may lead us to the

next step forward in the treatment of NSCLC with these targeted agents.

Since the toxicity profile of oral gefitinib is now well characterized, it was not the purpose of this analysis to evaluate toxicity. However, the majority of our patients tolerated gefitinib therapy well, with mild grade 1/2 rash and mild diarrhea being the most common toxicities. This is again consistent with the observations of the IDEAL 1 investigators.<sup>17</sup> Two hundred nine patients were evaluable for safety and tolerability in the IDEAL 1 trial, 103 of whom received gefitinib at the 250-mg dose level. In the cohort receiving the 250 mg/day dose, most adverse events were mild (CTC grade 1/2). There was no evidence of cumulative toxicity, and most were reversible. Adverse events were often seen before the end of the first month of treatment. In the 250-mg/day group, 15.5% of patients had adverse events requiring a short treatment interruption, and none required a dose reduction. The main reasons for dose interruptions were skin reactions, gastrointestinal disturbances, and elevated transaminases. Only 1.9% of patients stopped treatment because of these events. Twenty-four percent of patients on the 250-mg/day regimen took antipropulsive or antidiarrheal agents, and diarrhea resolved in 84% of patients. Skin disorders, including rash, pruritus, dry skin, and acne, were generally mild. They usually resolved during treatment or with temporary therapy interruption, or following treatment cessation. Concurrent rash and diarrhea occurred in 15.5% of patients.

## Conclusions

Oral gefitinib at 250 mg/day demonstrated clinically significant activity in a pretreated group of patients enrolled in an expanded-access program. A selected "landmark" group of patients who had taken the drug for 12 weeks experienced a median survival of 8.8 months and a 1-year survival rate of 35%. These survival figures, similar to first-line doublet chemotherapy trials, may be in part secondary to selection of patients with relatively indolent tumor behavior or selection of patients with EGFR-dependent tumors or both. Innovatively designed clinical trials are necessary to further elucidate the role of gefitinib and other similar agents in the treatment of NSCLC.

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