Clinical Course of Patients with Non–Small Cell Lung Cancer and Epidermal Growth Factor Receptor Exon 19 and Exon 21 Mutations Treated with Gefitinib or Erlotinib

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Abstract

Purpose: In patients with non–small cell lung cancer (NSCLC), mutations in the epidermal growth factor receptor (*EGFR*) tyrosine kinase domain have been associated with sensitivity to erlotinib and gefitinib. We undertook this study to explore the relationship between *EGFR* mutation type and clinical variables, including treatment with gefitinib and erlotinib.

Experimental Design: In patients with NSCLC, *EGFR* exon 19 deletion mutations and *EGFR* L858R point mutations were analyzed by nonsequencing PCR-based methods from paraffin blocks of tissue obtained before treatment. The results were correlated with clinical information (sex, pathologic subtype, race/ethnicity, treatment, and overall survival).

Results: The two most common *EGFR* mutations were identified in 24% (70 of 291; 95% confidence interval, 26%-38%) of tumors from patients with NSCLC. *EGFR* mutation was associated with Asian ethnicity ($P = 0.0023$) and being a "never smoker" ($P = 0.0001$). Among patients with *EGFR* mutations, 39% (27 of 70) had *EGFR* L858R, whereas 61% (43 of 70) had an *EGFR* exon 19 deletion. After treatment with erlotinib ($n = 12$) or gefitinib ($n = 22$), patients with *EGFR* mutations had a median overall survival of 20 months. After treatment with erlotinib or gefitinib, patients with *EGFR* exon 19 deletions had significantly longer median survival than patients with *EGFR* L858R (34 versus 8 months; log-rank $P = 0.01$).

Conclusions: *EGFR* mutations in exons 19 or 21 are correlated with clinical factors predictive of response to gefitinib and erlotinib. Those with *EGFR* exon 19 deletion mutations had a longer median survival than patients with *EGFR* L858R point mutation. These observations warrant confirmation in a prospective study and exploration of the biological mechanisms of the differences between the two major *EGFR* mutations.

Gefitinib and erlotinib target the EGFR tyrosine kinase detectable in most non–small cell lung cancers (NSCLC). Phase II and III trials have shown partial responses in 8% to 12% of unselected patients with progressive NSCLC after chemotherapy (1–4). Somatic mutations in the epidermal growth factor receptor (*EGFR*) gene have been identified in patients with radiographic responses to the EGFR tyrosine kinase inhibitors (TKI) gefitinib and erlotinib (5–7). Before this association with *EGFR* mutation, a number of clinical factors had been correlated with response to gefitinib or erlotinib, including never smoking status, female sex, Asian ethnicity, and adenocarcinoma histology (especially bronchioloalveolar subtype; refs. 1, 8, 9). Now, after DNA from a large number of tumors have been sequenced for mutations in the tyrosine kinase domain of *EGFR*, significant associations between clinical factors predicting response to gefitinib and *EGFR* mutations have been confirmed in most series (6, 7, 10–16).

Although many *EGFR* mutations have been reported, not all have been associated with responsiveness to gefitinib and erlotinib. The two most common *EGFR* mutations that have been identified, representing 85% to 90% of *EGFR* mutations, are the *EGFR* exon 19 deletion that eliminates a leucine-arginine-glutamate-alanine motif in the tyrosine kinase domain of *EGFR* and a thymine-to-guanine transversion that results in an arginine for leucine substitution at amino acid 858 (L858R). Shortly after the identification of *EGFR* mutations associated with response to erlotinib or gefitinib, we developed an assay for *EGFR* exon 19 deletion and *EGFR* L858R suitable for routine clinical use with greater sensitivity than standard sequencing-based assays (17).

This study was undertaken to explore the relationship between *EGFR* mutation status and clinical variables, including treatment with EGFR TKIs, and to compare outcomes between patients with the two most common *EGFR* mutations. Here, we

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report the results of *EGFR* genotyping of patients with NSCLC from Memorial Sloan-Kettering Cancer Center and examine clinical factors associated with the two most common *EGFR* mutations. We compare the clinical and pathologic features of patients with *EGFR* mutations that have been associated with responsiveness to gefitinib and erlotinib and correlate mutation type with survival after treatment with these agents.

Materials and Methods

Patients and clinical characteristics. We have included all patients with NSCLC on whom successful *EGFR* genotyping was done in the Laboratory of Diagnostic Molecular Pathology at Memorial Sloan-Kettering Cancer Center. The results of the *EGFR* mutational analysis, tumor stage, pathologic subtype, and survival were obtained by retrospective chart review. The reported age is the age at diagnosis with NSCLC. Sex and race/ethnicity were determined by patient self-report at the time of initial registration at this institution. Stage at presentation was determined using current American Joint Committee on Cancer staging criteria (18). Histology was obtained from the pathology report corresponding to the specimen sent for *EGFR* genotype analysis. Smoking history was determined by review of the medical records, including both physician description of smoking history and an institutional smoking history questionnaire completed by the patient. Patients described as receiving treatment with erlotinib or gefitinib were determined by review of the medical record. Those patients who had smoked <100 cigarettes in their lifetime were categorized as never smokers. Those patients who smoked cigarettes within 1 year of the diagnosis were categorized as current smokers. The review of records was done under a waiver of authorization approved by the MSKCC Privacy Board. Survival time and progression-free survival were calculated from the date of initiation of erlotinib or gefitinib. Patients who were not deceased were censored at the date of last contact with this institution. This date was verified by inpatient and outpatient medical records and/or confirmation with the patient's primary physician. Included within this analysis are 60 patients whose mutation status has been previously reported (19).

Mutational analysis. Tumor specimens were not routinely microdissected before mutational analysis. In some cases where only a small focus of tumor was present in the block, manual microdissection was done. *EGFR* exon 19 deletions were studied by length analysis of fluorescently labeled PCR products on a capillary electrophoresis device, using the following primers: EGFR-Ex19-FWD1, 5′-GCACCATCTCACAATTGCCAGTTA-3′ and EGFR-Ex19-REV1, 5′-Fam-AAAAGGTGGGCCTGAGGTTCA-3′. The cases were also screened for the exon 21 L858R mutation by a PCR RFLP assay, based on a new *Sau*96I restriction site created by the L858R mutation (2573T → G). The *Sau*96I-digested fluorescently labeled PCR products were analyzed by capillary electrophoresis, and the following primers were used: EGFR-Ex21-FWD1, 5′-CCTCACAGCAGGGTCTTCTCTGT-3′ and EGFR-Ex21-REV1, 5′-Fam-TCAGGAAAATGCTGGCTGACCTA-3′ (17). These assays reliably detect mutations in mixtures containing as little as 5% to 10% tumor DNA (17). Direct sequencing of *EGFR* was also done in some cases, as previously described (7). In such cases, all sequencing reactions were done in both forward and reverse directions, and all mutations were confirmed by PCR amplification of an independent DNA isolate.

Statistical Analysis. The variables measured in the study were investigated for association using the Fisher's exact test when two categories existed for a variable and Pearson's χ^2 test when three or more categories existed for a variable. Statistical significance was determined by a two-tailed $P < 0.05$. Median duration of overall survival and progression-free survival were calculated using the Kaplan-Meier method. Comparison of survival between groups was made using the log-rank test. Survival analysis was done using Stata version 8 for Windows.

Results

Relationship between presence of EGFR mutations and clinicopathologic features. NSCLC tumors from 291 patients were examined for the presence of the two most common *EGFR* mutations associated with response to erlotinib or gefitinib. Seventy patients (24%) were found to have either *EGFR* exon 19 deletion or *EGFR* L858R. The clinical characteristics of patients tested for *EGFR* mutations are listed in Table 1. Univariate analyses showed an association between *EGFR* mutation and both never smoker status ($P = 0.0001$) and self-reported Asian race/ethnicity ($P = 0.0023$). There was no association with female gender ($P = 0.31$). No correlation of *EGFR* mutation with pathologic subtype was found, but the large majority of patients tested for *EGFR* mutation had adenocarcinoma or adenocarcinoma with bronchioloalveolar carcinoma features (20). One patient with squamous and another with adenosquamous tumor histology were found to have an *EGFR* exon 19 deletion. Of the 70 patients with mutations, 32 patients were former or current smokers. These smokers had a median smoking history of 9 pack-years (range, 0-75 pack-years). Three patients with ≥70 pack-year history of smoking were found to have *EGFR* mutations.

Correlation of EGFR genotype with clinicopathologic features. Of the 70 patients with an *EGFR* mutation, 43 (61%) had an *EGFR* exon 19 deletion and 27 (39%) had an *EGFR* L858R mutation. The clinical characteristics of this group are shown in Table 2. When comparing patients whose tumors had an *EGFR* exon 19 deletion to *EGFR* L858R, there was no significant difference in the proportion of women (26 of 43 versus 18 of 27; $P = 0.62$), Asians (4 of 43 versus 3 of 27; $P = 1.0$), African Americans (4 of 43 versus 2 of 27; $P = 1.0$), never smokers (24 of 43 versus 14 of 27; $P = 0.8$), or adenocarcinoma histology (37 of 43 versus 27 of 27; $P = 0.07$).

Correlation of EGFR genotype with clinical course during treatment with gefitinib or erlotinib. Thirty-four of the 70 patients with *EGFR* exon 19 deletion or *EGFR* L858R had been treated with either gefitinib or erlotinib. The remaining 36 patients either were not available for follow-up ($n = 6$) or did not receive treatment because all sites of disease were surgically resected ($n = 30$). The median time from initial lung cancer diagnosis to beginning either erlotinib ($n = 12$) or gefitinib ($n = 22$) was 17 months (95% confidence interval, 4-25 months). Patients who presented with early-stage disease and subsequently experienced disease recurrence ($n = 9$) had a median time to recurrence of 15 months. From the diagnosis of recurrent/metastatic disease, the median time to treatment was 9 months for erlotinib-treated patients and 10 months for those patients treated with gefitinib. Among these patients with *EGFR* mutations, the median progression-free survival after initiation of gefitinib or erlotinib was 12 months (95% confidence interval, 8 months to not reached; range, 3 to ≥29 months), and the median overall survival after initiation of gefitinib or erlotinib was 20 months (95% confidence interval, 16 months to not reached; range, 4 to ≥34 months). Comparison of patients treated with erlotinib to those treated with gefitinib revealed no difference in overall survival (log-rank $P = 0.54$).

To explore whether the two major *EGFR* mutation genotypes respond differently to treatment with gefitinib and erlotinib, we determined the progression-free survival and overall survival of patients with these genotypes from the time of initiation of

Table 1. Patient characteristics

	Wild-type *EGFR* (n = 221)	Mutated *EGFR* (n = 70)	P
Age			
Median	65	62	
Mean	63	61	
Range	30-85	41-85	
Sex			
Male	70 (32%)	27 (39%)	
Female	151 (68%)	43 (61%)	0.31
Stage at presentation			
I	87 (39%)	16 (23%)	
II	11 (5%)	2 (3%)	
III	29 (13%)	12 (17%)	
IV	94 (43%)	40 (57%)	
Histology			
Adenocarcinoma	105 (48%)	35 (50%)	
AWBF	79 (36%)	24 (34%)	
BAC	20 (9%)	4 (6%)	
Adenosquamous	4 (2%)	1 (1%)	
Squamous	4 (2%)	1 (1%)	
Other	9 (4%)	5 (7%)	
Smoking			
Former	131 (59%)	30 (43%)	
Current	54 (24%)	2 (3%)	
Never	36 (16%)	38 (54%)	0.0001
Smoking history			
Never	36 (16%)	38 (54%)	
≤5	15 (7%)	7 (10%)	
6-10	13 (6%)	11 (16%)	
11-15	6 (3%)	2 (3%)	
16-25	18 (8%)	2 (3%)	
26-50	62 (28%)	3 (4%)	
51-75	27 (12%)	1 (1%)	
>75	29 (13%)	2 (3%)	
Unknown	15 (7%)	4 (6%)	
Race/ethnicity			
Asian	3 (1%)	7 (10%)	0.002
African American	8 (4%)	6 (9%)	0.10
Hispanic	2 (1%)	1 (1%)	
White/non-Hispanic	204 (92%)	55 (79%)	
Not reported	5 (2%)	1 (1%)	
Treated with EGFR TKI			
Yes	50 (23%)	34 (49%)	
No	171 (77%)	36 (51%)	

Abbreviations: BAC, bronchioloalveolar carcinoma; AWBF, adenocarcinoma with bronchioloalveolar carcinoma features.

treatment (Fig. 1). In this subset of patients, there was no significant difference in proportion of women, never smokers, adenocarcinoma histology, or bronchioloalveolar carcinoma features (Table 3). At the time of initiation of treatment, whereas patients with *EGFR* exon 19 deletion were more likely to have a site of at least one extrathoracic metastasis (14 of 23 versus 2 of 11; P = 0.03), there was no significant difference in the incidence of metastases to individual sites of bone, brain, or liver. There was no significant difference in the baseline Karnofsky performance status of these patients. Patients with *EGFR* exon 19 deletion had a median progression-free survival of 12 months compared with 5 months for patients with *EGFR* L858R (P = 0.01). Patients with *EGFR* exon 19 deletion had a median overall survival of 34 months compared with 8 months for patients with *EGFR* L858R (P = 0.01).

Correlation of overall survival with smoking history in patients with EGFR mutations. Of the patients with *EGFR* mutations who had been treated with gefitinib or erlotinib and were former or current smokers, the median smoking history was 8 pack-years. For these patients, we compared the overall survival of patients who were never smokers (n = 16), of former smokers who had smoked less than the median smoking history of <8 pack-years (n = 8), and of those who had smoked ≥8 pack-years (n = 10; Fig. 2). The median overall survival for never smokers was 20 months. The median survival of former smokers who smoked <8 pack-years has not been reached, whereas the median survival of former smokers with ≥8 pack-year history of smoking was 8 months.

Discussion

Our retrospective review of the results of *EGFR* mutation analysis done as part of clinical care of patients with NSCLC represents the largest group of patients from North America for which tumor *EGFR* genotyping has been reported. In addition to correlating *EGFR* mutations with clinical factors predictive of response to erlotinib or gefitinib, we found that patients with *EGFR* exon 19 deletions had longer overall survival when compared with patients with *EGFR* L858R after treatment with erlotinib or gefitinib (P = 0.01).

We report a relatively high proportion (24%) of patients with one of the two most common *EGFR* mutation genotypes. As

Table 2. Characteristics of patients with *EGFR* exon 19 deletion or *EGFR* L858R

	Exon 19 deletion (n = 43)	L858R (n = 27)
Age		
Median	60	66
Range	41-81	43-85
Sex		
Female	26	18
Male	17	9
Smoking		
Former	18	12
Current	1	1
Never	24	14
Histology		
Adenocarcinoma	22	13
AWBF	11	13
BAC	4	0
Other	6	1

Abbreviations: BAC, bronchioloalveolar carcinoma; AWBF, adenocarcinoma with bronchioloalveolar carcinoma features.

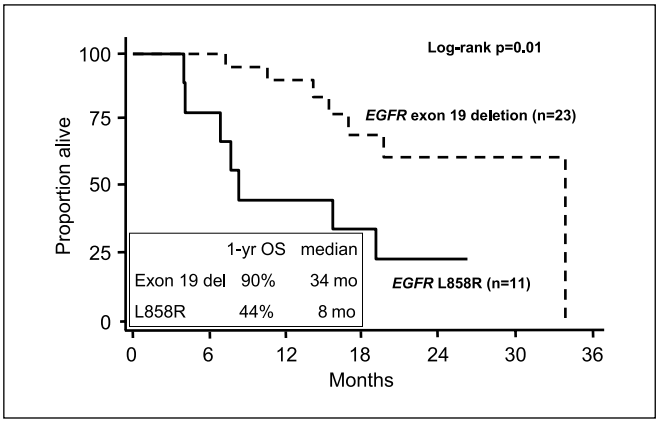

Fig. 1. Overall survival by *EGFR* mutation.

clinical factors predictive of sensitivity to EGFR TKIs antedated identification of *EGFR* mutations, clinicians tended to request mutational studies of patients with such factors. The group of patients studied is enriched for never smokers, women, patients with adenocarcinoma, and patients of Asian ethnicity. Only 8% (24 of 291) patients tested had nonadenocarcinoma histology. Additionally, this series has a relatively large proportion of patients who presented with metastatic disease. Many of the previous series were made up almost solely of patients who had resections for early-stage NSCLC.

Multiple prior international reports have confirmed the association of mutations with those clinical characteristics known to predict response to gefitinib or erlotinib (i.e., Asian ethnicity, history of never smoking, and adenocarcinoma histology). In this large group of patients from North America, we confirmed the association of *EGFR* mutation with some of the clinical predictors of response, including history as a never smoker and Asian ethnicity. Women were not more likely to have tumors with *EGFR* mutations in this series that included a disproportionate number of women (51% of patients with NSCLC referred to our medical oncology service are women). This observation has been made by other groups as well. However, some have found gender to be predictive in multivariate analyses.

Since the initial reports of partial responses with gefitinib, researchers have noted a significant geographic and ethnic variability in the sensitivity of patients to this class of agents. After the identification of somatic mutations in *EGFR* and their association with response, it became clear that these two factors were linked. A significantly higher proportion of patients from East Asia have mutations in *EGFR* based on multiple reports from Japan, China, Taiwan, and Europe, as well as smaller studies from North America. Accordingly, obtaining accurate information about each patient's country of origin, race, and ethnicity is vital. In contrast to a previous report that noted a relatively low incidence of *EGFR* mutations in patients of African-American ethnicity (2%, 1 of 41), 43% (6 of 14) of African-American patients in our series had *EGFR* mutations. Clearly, a variety of factors could modify this incidence with the most obvious being smoking history. Fifty-seven percent (8 of 14) of African-American patients in our series were never smokers.

These data extend the observation that a heavy smoking history in patients with NSCLC is associated with a poorer survival to this subpopulation of NSCLC patients with *EGFR* mutations (21, 22). The cause of this difference is not fully understood, although repeated exposure to tobacco-related carcinogens is thought to lead to a more genetically complex tumor in patients with heavy smoking history. Although *EGFR* mutations and *KRAS* mutations, the most well-studied genetic lesion in smokers, are thought to be mutually exclusive, it remains possible that other mutations caused by tobacco-related carcinogens may be present in heavy smokers and lead to decreased overall survival (23). More comprehensive molecular analysis of tumors from patients with NSCLC and *EGFR* mutations will be helpful to clarify this issue.

Many recent series have compared NSCLC patients with *EGFR* mutations to those patients with no detectable *EGFR* mutations to explore the clinical relevance of *EGFR* mutations for sensitivity to gefitinib or erlotinib. Some series show an

Table 3. Baseline characteristics of patients with metastatic NSCLC with *EGFR* mutations treated with EGFR-TKI

	All (n = 34)	Exon 19 deletion (n = 23)	L858R (n = 11)	P
Age				
Median	64	60	64	
Range	41-80	41-74	48-80	
Sex				
Female	20	11 (48%)	9 (82%)	0.08
Male	14	12 (52%)	2 (18%)	
Smoking				
Former/Current	18	11 (48%)	6 (55%)	1.00
Never	16	12 (52%)	5 (45%)	
Histology				
Adenocarcinoma	18	9 (39%)	9 (81%)	0.11
AWBF	10	8 (35%)	2 (18%)	
BAC	3	3 (13%)	0 (0%)	
Other	3	3 (13%)	0 (0%)	
KPS at start of TKI				
80-100%	22	15 (65%)	7 (64%)	0.91
60-70%	5	3 (13%)	2 (18%)	
not recorded	7	5 (22%)	2 (18%)	
Prior chemotherapy				
0	16	10 (44%)	6 (55%)	1.00
1	10	7 (30%)	3 (27%)	
2	4	3 (13%)	1 (9%)	
≥3	4	3 (13%)	1 (9%)	
Drug received				
Erlotinib	12	8 (35%)	4 (36%)	1.00
Gefitinib	22	15 (65%)	7 (64%)	
Metastatic sites				
Bone	11	9 (39%)	2 (18%)	0.53
Brain	5	5 (22%)	0 (0%)	
Liver	4	4 (17%)	0 (0%)	
Other extrathoracic	2	2 (9%)	0 (0%)	

Abbreviations: BAC, bronchioloalveolar carcinoma; AWBF, adenocarcinoma with bronchioloalveolar carcinoma features; KPS, Karnofsky performance status.

improvement in overall survival for patients with *EGFR* mutations who have been treated with gefitinib or erlotinib (10, 24). Mitsudomi et al. studied 59 patients with disease recurrence after surgery who had been treated with gefitinib (25) and found that patients with *EGFR* mutations had a prolonged survival ($P = 0.005$). Similarly, Chou et al. examined 54 patients, 61% of whom had mutations in *EGFR* and showed longer progression-free survival ($P = 0.011$) and overall survival ($P = 0.046$) after treatment with gefitinib when compared with patients with wild-type *EGFR* (26). Cappuzzo et al., in examining a group of 89 patients who had been treated with gefitinib, found 15 patients with mutations in *EGFR* with a median survival of 21 months as opposed to a median survival of 8 months for the 74 patients without mutations ($P = 0.09$; ref. 27). Similarly, Tokumo et al. looked at 21 gefitinib treated patients, 9 with mutations in *EGFR*, and noted a 25-month survival for patients with mutations and 14 months for those without mutations ($P = 0.15$; ref. 15). A variety of pitfalls are associated with comparing patients with *EGFR* mutations to those without detectable mutations, including potential sensitivity issues in the use of direct sequencing to detect *EGFR* mutations (whereby patients with *EGFR* mutations are included in the wild-type group) and the uncertainty of association of *EGFR* mutations other than exon 19 deletions and L858R with response to erlotinib or gefitinib. To avoid these problems, our survival analysis included only patients with detectable mutations and compared the two most common subtypes of mutations, *EGFR* L858R and *EGFR* exon 19 deletion.

Our results suggest that specific *EGFR* mutation genotypes may be predictive of survival after treatment with *EGFR* TKI in patients with NSCLC, showing that *EGFR* exon 19 deletion patients treated with erlotinib or gefitinib lived longer than patients with *EGFR* L858R ($P = 0.01$). This survival benefit was observed in spite of the higher frequency of extrathoracic metastases for patients with *EGFR* exon 19 deletions. A previous report of patients treated with gefitinib or erlotinib noted a difference in response rate, which favored patients with *EGFR* exon 19 deletion, but differences in survival were not detected (25). Mitsudomi et al. noted a 62% (8 of 13) response rate in patients with *EGFR* point mutations compared with 100% (16 of 16) response rate in patient with *EGFR* exon 19 deletion ($P = 0.0108$). In contrast, Shigematsu et al. reported data from patients, never treated with EGFR TKI, who had surgically resected NSCLC (14). They compared 62 patients with *EGFR* mutations (31 with *EGFR* L858R and 31 with *EGFR* exon 19 deletion) and noted a relatively prolonged survival for those patients with L858R ($P = 0.05$). If prospectively confirmed, our data suggest that treatment with gefitinib or erlotinib alters the natural history of patients with *EGFR*-mutated NSCLC, converting the *EGFR* exon 19 deletion subtype of NSCLC from a disease with a worse prognosis to one with a more favorable prognosis.

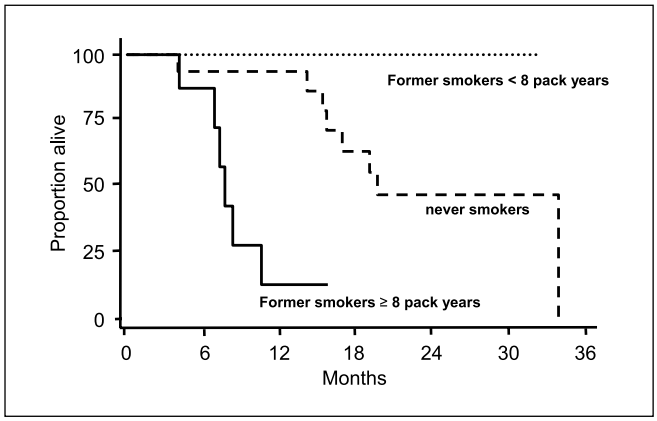

Fig. 2. Overall survival by smoking history.

Differences in response rate determined by different mutations and prolonged survival for TKI therapy has also been observed with imatinib in the treatment of patients with gastrointestinal stromal tumors. After the initial identification of *KIT* mutations and their association with response to imatinib, it was noted that particular mutations conferred greater sensitivity to imatinib (28–30). Recently, an analysis of tumor specimens from an intergroup trial of imatinib showed a longer time to treatment failure and overall survival in patients with *KIT* exon 9 mutations compared with those patients with *KIT* exon 11 mutations (31).

Our data highlight the need for a prospective analysis of *EGFR* genotype in a larger study of patients treated with erlotinib or gefitinib. Unfortunately, recent results of *EGFR* genotyping from the largest trial of erlotinib to date suffered from low levels of tissue acquisition, obtaining usable tissue for *EGFR* sequence analysis on only 177 patients of 731 patients randomized, and a relatively low total number of mutations identified ($n = 40$, of which only 21 were L858R mutations or exon 19 deletions, the mutations previously associated with sensitivity to erlotinib), making analysis of these data problematic (32). Future analyses should incorporate the prospective collection of tumor blocks and an attempt to correlate other factors, which may be predictive of response to gefitinib or erlotinib, including *EGFR* amplification, EGFR expression, *KRAS* mutations, and phospho-AKT expression (27).

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