Effects of Erlotinib in EGFR Mutated Non-Small Cell Lung Cancers with Resistance to Gefitinib


Abstract

Purpose: Most lung cancers with activating epidermal growth factor receptor (EGFR) mutations respond to gefitinib; however, resistance to this tyrosine kinase inhibitor (TKI) invariably ensues. The T790M mutation occurs in 50% and MET amplification in 20% of TKI-resistant tumors. Other secondary mutations (D761Y and L747S) are rare. Our goal was to determine the effects of erlotinib 150 mg/d in EGFR mutated patients resistant to gefitinib 250 mg/d, because the EGFR TKI erlotinib is given at a higher biologically active dose than gefitinib.

Experimental Design: Retrospective review of 18 EGFR mutated (exon 19 deletions, L858R, and L861Q) patients that were given gefitinib and subsequently erlotinib. Seven patients had tumor resampling after TKI therapy and were analyzed for secondary EGFR mutations and MET amplification.

Results: Most patients (14 of 18) responded to gefitinib with median progression-free survival of 11 months (95% confidence interval, 4-16). After gefitinib resistance (de novo or acquired), 78% (14 of 18) of these patients displayed progressive disease while on erlotinib with progression-free survival of 2 months (95% confidence interval, 2-3). Six of 7 resampled patients acquired the T790M mutation, and 0 of 3 had MET amplification. Only 1 gefitinib-resistant patient with the acquired L858R-L747S EGFR, which in vitro is sensitive to achievable serum concentrations of erlotinib 150 mg/d, achieved a partial response to erlotinib.

Conclusions: In EGFR mutated tumors resistant to gefitinib 250 mg/d, a switch to erlotinib 150 mg/d does not lead to responses in most patients. These findings are consistent with preclinical models, because the common mechanisms of TKI resistance (T790M and MET amplification) in vitro are not inhibited by clinically achievable doses of gefitinib or erlotinib. Alternative strategies to overcome TKI resistance must be evaluated.

In 2008, lung cancer continues to lead cancer-related deaths in the United States for both men and women (1). Non-small cell lung cancers (NSCLC) comprise the majority of cases, and the prognosis of patients diagnosed with advanced NSCLC continues to be dismal (2). Use of palliative platinum-based chemotherapy has been the standard therapy for NSCLC (3). However, even the addition of the vascular endothelial growth factor monoclonal antibody bevacizumab (4) to chemotherapy can only achieve response rates of 30%, progression-free survival (PFS) of <8 months and the median overall survival (OS) barely reaches 12 months. Despite three Food and Drug Administration-approved second-line therapies for platinum-resistant NSCLC, which are docetaxel (5), pemetrexed (6), and erlotinib (7), very few patients survive for longer than 2 years. Nonetheless, there is great heterogeneity between patients and their clinical course and response to different anticancer therapies.

The identification of somatic mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene in patients with NSCLC provided one of the first examples of...
EGFR mutated NSCLC are sensitive to EGFR inhibitors in preclinical models. Clinical experience with the use of gefitinib/erlotinib in EGFR mutated patients indicates that many exon 19 deletion and L858R-bearing tumors display responses that sometimes reach a year; however, acquired resistance to EGFR TKIs invariably develops. The secondary T790M mutation occurs in 50% and amplification of MET in 20% of TKI-resistant tumors. Few other secondary mutations (D761Y and L747S) have been described. Few therapies have been studied for the expanding number of EGFR mutated tumors that become resistant to gefitinib. Our data indicate that in EGFR mutated patients with resistance to gefitinib 250 mg/d, a switch to erlotinib 150 mg/d does not lead to radiographic responses in most patients despite the higher biologically active dose of erlotinib. Only a patient with the acquired L858R-L747S responded to erlotinib. Preclinical models indicated that the two most common mechanisms of acquired resistance to gefitinib, EGFR-T790M and MET amplification, are highly resistant to achievable clinical concentrations of erlotinib, whereas L858R-L747S is sensitive to erlotinib at 150 mg/d. The correlation of our findings with the molecular understanding of sensitivity and resistance of EGFR mutated systems underlines the need for genotype-based clinical studies to advance our understanding of treatment of this representative patient cohort.

Potential patient-tailored therapy in this disease (8–10). Large-scale sequencing efforts have consistently identified EGFR mutations in an enriched cohort of women, never smokers, adenocarcinomas, and East Asians (11). The most prevalent EGFR mutations consist of small in-frame deletions around the conserved LREA motif of exon 19 (residues 747-750) followed by a single point mutation (L858R) in exon 21 (12, 13). Both cell line and mouse models of EGFR mutations show that tumor cells that harbor such mutations are exquisitely sensitive to EGFR inhibition (9, 14, 15). The aforementioned models have identified that EGFR-driven lung cancers are “addicted” to EGFR signaling for their survival and proliferation. More so, EGFR mutations are oncogenic and alter the tyrosine kinase pocket of EGFR to a degree that enhances the sensitivity to ATP-competitive EGFR inhibitors (16). Both these factors make EGFR mutated NSCLC more sensitive to EGFR tyrosine kinase inhibitors (TKI).

Retrospective studies of thousands of patients treated with the two currently available anilinoquinazoline small-molecule EGFR TKIs, gefitinib and erlotinib, as second- or third-line therapies in NSCLC (17, 18), showed that a majority (close to 80%) of patients with classic EGFR mutant tumors attain radiographic and clinical responses to these oral agents. In some series, both PFS and OS were significantly better for EGFR TKI-treated patients with EGFR mutations when compared with wild-type cases (17). The evaluation of EGFR mutation as a prognostic and predictive marker is NSCLC is under way, with multiple phase II and III trials analyzing this biomarker. Seven prospective phase II trials have evaluated gefitinib monotherapy for patients selected based on their EGFR mutational status (19–21). These have confirmed that ~75% of patients with L858R or exon 19 deletion mutations achieve responses.

Despite the efficacy of gefitinib monotherapy for EGFR-mutant NSCLC, acquired resistance to EGFR TKI therapy is seen in most patients. In almost all prospective trials, the PFS did not exceed 12 months (19). The secondary resistant T790M mutation (22, 23) arises most often in cis to L858R or exon 19 deletions in ~50% of patients with radiographic progression (24, 25). The acquired amplification of the MET oncogene occurs in ~20% of gefitinib/erlotinib-resistant patients and in half of these cases in conjunction with T790M (26, 27). The mechanisms of resistance in the remaining tumors have not been completely clarified and very few other secondary mutations, such as L858R-D761Y (24) and L858R-L747S (28, 29), identified in gefitinib-progressive specimens.

The management of this growing population of EGFR TKI-resistant NSCLC is not established, but the success of any approach will likely be dependent on the mechanism of acquired resistance of the tumor. In other “oncogene-addicted” tumors, such as chronic myeloid leukemia and gastrointestinal stromal tumors, where the BCR-ABL translocation or c-KIT mutations, respectively, make these cancers sensitive to imatinib, it seems that the dose of the TKI matters (30). In both disorders, one clinical step when resistance emerges is to increase the dose of imatinib from 400 to ≥600 mg/d (31–33). This dose escalation maneuver is only effective in some patients, possibly by inhibiting secondary mutations with borderline resistance to imatinib or by affecting nonmutation dependent mechanisms, with short periods of disease control (31, 33). Second-generation ABL and KIT inhibitors have gained momentum and recently received Food and Drug Administration approval as alternative therapies (34, 35).

In EGFR mutated tumors, it is unknown if EGFR TKI dose escalations, in the face of acquired or de novo resistance, changes the course of TKI-progressive tumors. To evaluate the efficacy of such approach, we retrospectively studied the course of EGFR mutated patients that first received gefitinib 250 mg/d and on becoming gefitinib-resistant were exposed to erlotinib 150 mg/d. This gefitinib to erlotinib switch is predicted to expose patients to almost double the biologically active dose of an EGFR TKI (36, 37). Because EGFR-T790M and MET amplification lead to high level of in vitro resistance to both gefitinib and erlotinib (22, 27), we hypothesized that erlotinib should only alter the response of acquired borderline resistant clones carrying the rare L858R-D761Y or L858R-L747S gefitinib-resistant mutations.

Materials and Methods

Patient selection. Patients were identified from the databases of five academic medical centers: (a) Beth Israel Deaconess Medical Center, (b) Dana-Farber Cancer Institute, (c) Massachusetts General Hospital, (d) Memorial Sloan-Kettering Cancer Center, and (e) Yonsei University College of Medicine. Inclusion criteria to use the patient’s data included signed informed consent for EGFR mutation analysis, an institutional approved protocol for human studies and genomic analysis of stored tumor tissue, a diagnosis of stage IV metastatic NSCLC with a proven EGFR mutation, and the exposure to both gefitinib and erlotinib. Gefitinib at an initial dose of 250 mg/d had to be given as the first EGFR TKI therapy and erlotinib at a starting dose of 150 mg/d subsequently to progression on gefitinib. We did not exclude patients that had received investigational compounds between gefitinib and erlotinib to maximize
Results

Patient characteristics. After a review of EGFR genotyped patients in our centers from 2004 to 2008, we identified 18 EGFR mutated patients that had received gefitinib and erlotinib. Clinical, demographic, pathologic, and molecular characteristics of this cohort are displayed in Table 1. Sixty-one percent of patients were women (11 of 18) and the majority never smokers (11 of 18). Ages varied between 43 and 80 years (Table 1). Almost all (16 of 18) patients had adenocarcinoma as the main histologic type of their tumor. These characteristics are similar to historic cohorts of EGFR mutated tumors (17). Exon 19 deletion-containing tumors were found in 13 (72%) patients, L858R mutations in 4 (22%) patients, and L861Q in 1 patient (Table 1).

Of the studied patients, 8 received gefitinib as their first anticancer therapy (44%) and 10 had received platinum-based chemotherapy previously (56%). Most patients (15 of 18, 83%) were not exposed to any other form of therapy between stopping gefitinib and before receiving erlotinib (Tables 1 and 2).

Initial response to gefitinib 250 mg/d. Fourteen of the 18 (78%) patients had radiographic responses to gefitinib (Table 2), a number that is compatible with retrospective and prospective data for EGFR mutated patients (11, 19, 44). Two (11%) patients had stable disease (SD), and another 2 patients had de novo resistance to gefitinib with progressive disease (PD) as best response.

Response to erlotinib 150 mg/d. Patients were given erlotinib at an initial dose of 150 mg/d after their tumors had become gefitinib-resistant. The majority of patients had no additional systemic therapy between gefitinib and erlotinib (Table 1).

Fourteen of the 18 (78%) patients had PD as the best response to erlotinib monotherapy, an additional 3 (16%) patients had brief periods of SD as best response, and only 1 (6%) patient had a radiographic partial response (PR; Tables 2 and 3).

Median PFS was 2 months, with a 95% CI of 2 to 3 months (Fig. 2). Only 2 (11%) patients, one each with PR and SD, remained on erlotinib without progression for over 5 months and no patient had a PFS of over 6 months (Table 2). PFS was similar for patient that had or had not received chemotherapy.

Table 1. Clinical, pathologic, demographic, and molecular characteristics of the studied EGFR mutated patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>63</td>
</tr>
<tr>
<td>Range</td>
<td>43-80</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Male</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Smoker</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>16 (89)</td>
</tr>
<tr>
<td>NSCLC-not otherwise specified</td>
<td>2 (11)</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletion*</td>
<td>13 (72)</td>
</tr>
<tr>
<td>L858R</td>
<td>4 (22)</td>
</tr>
<tr>
<td>L861Q</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Therapy before gefitinib</td>
<td></td>
</tr>
<tr>
<td>Platinum-based chemotherapy</td>
<td>10 (56)</td>
</tr>
<tr>
<td>No prior therapy</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Therapy in between gefitinib and erlotinib</td>
<td></td>
</tr>
<tr>
<td>Experimental agent</td>
<td>3 (17)</td>
</tr>
<tr>
<td>No therapy</td>
<td>15 (83)</td>
</tr>
</tbody>
</table>

*Specific EGFR sequences of the exon 19 deletions are detailed in Table 2.
as their first line of systemic therapy (Table 2). Four of 14 (29%) gefitinib responders had PR or SD after erlotinib compared with 0 of 4 gefitinib nonresponders. All 4 of the gefitinib nonresponders progressed on erlotinib by 2 months, whereas half of the gefitinib responders had not progressed by 2 months.

**EGFR resequencing after progression on EGFR TKI therapy and subsequent response to erlotinib.** Seven of the 18 patients had their tumors sampled after progression on EGFR TKI therapy: 3 after gefitinib therapy and the other 4 after gefitinib and erlotinib. Of these patients, 6 of 7 (86%) had acquired the T790M mutation in association with their initial activating L858R or exon 19 deletions. Five of the 6 (83%) T790M-carrying tumors displayed PD to erlotinib therapy (Table 2). One patient with exon 19 deletion (delE746-A750)-T790M had 6 months of SD on erlotinib; however, because a biopsy was obtained after gefitinib and erlotinib, we cannot exclude the possibility that T790M was acquired while on erlotinib therapy. One patient had acquired the L747S secondary mutation in association with the activating L858R EGFR after exposure to gefitinib. The patient carrying L858R-L747S had a partial radiographic response to erlotinib 150 mg/d that lasted 6 months (Table 2).

**MET amplification after progression on EGFR TKI therapy.** Of the 7 patients that had their tumors sampled after progression on EGFR TKI therapy, 3 had sufficient material for analysis of MET amplification. None of these 3 had amplification of the MET oncogene. Patients 2 and 18 were analyzed by quantitative PCR methods and patient 6 was analyzed by fluorescence in situ hybridization (Table 2).

**OS from start of gefitinib.** The median OS of all 18 patients from start of gefitinib therapy to death was 30 months, 95% CI of 19 to 39 months. This is similar to OS reported for other series of EGFR mutated patients (17, 19).

**Discussion**

EGFR mutated cancers comprise a subset of NSCLC that are intrinsically sensitive to small-molecule EGFR inhibitors (12, 15, 17). The current clinical experience with the use of gefitinib and erlotinib in EGFR mutated patients indicates that exon 19 deletion and L858R-bearing tumors commonly display radiographic responses to these drugs with disease control durations that sometimes reach a year or longer (17, 19). Despite this unprecedented disease control rate, acquired resistance to EGFR TKIs invariably develops over the course of therapy and is becoming the main obstacle for management of this patient population (12). The first mechanism of acquired resistance described was the acquisition of the T790M mutation (22, 23). The methionine residue at position 790 generates a bulkier side chain that either affects binding of TKIs or enhances the affinity of the EGFR tyrosine kinase pocket to ATP, and this enhanced ATP affinity decreases the effective binding of gefitinib and erlotinib to the tyrosine kinase pocket of EGFR (22, 45). There is a great deal of similarities among structures of tyrosine kinase receptors and some analogous acquired resistance mutations fall exactly in the same amino acid residue. This is the case of the T315I, T670I, and T790M mutations in ABL1, KIT, and EGFR, respectively, in chronic myeloid leukemia, gastrointestinal stromal tumors, and EGFR mutated NSCLC (46). Our groups have shown in multiple in vitro and in vivo models that T790M in cis to an activating mutation (either L858R or exon 19 deletions) negates the sensitivity to achievable doses of gefitinib or erlotinib (23, 38).
The in vitro concentrations of gefitinib/erlotinib that can inhibit T790M-EGFR and T790M-carrying cells exceed 5 to 10 μmol/L (22, 23, 38, 46). Very few other secondary EGFR mutations have been described (24, 28). These have only been seen in patients receiving gefitinib who carried the L858R mutation. L858R-L761Y (24) and L858R-L747S (28) in vitro shift the sensitivity curves for gefitinib and erlotinib when compared with L858R alone; however, both mutations are 100-fold less “resistant” than L858R-T790M or exon 19 deletion-T790M. Most in vitro data would suggest that L858R-D761Y and L858R-L747S would be inhibited if the EGFR TKI dose reached 1 to 2 μmol/L (24, 28), which is achievable with 150 mg/d erlotinib but not with 250 mg/d gefitinib. The clinical dose of gefitinib of 250 mg/d is far less than its maximum tolerated dose of 1,000 mg/d. The mean steady-state serum concentration of gefitinib following 225 mg/d varied from 0.03 to 0.32 μg/mL in a phase I trial (36), with an average of 0.16 μg/mL or 0.358 μmol/L. The mean concentration increases to 0.24 μg/mL at 300 mg/d and to 1.1 μg/mL or 2.461 μmol/L at 1,000 mg/d gefitinib (36). Erlotinib is used clinically at a dose of 150 mg/d (7), which is its maximum tolerated dose. The steady-state trough concentrations at this dose ranged from 0.33 to 2.64 μg/mL in the phase I trial (37), with a median of 1.26 μg/mL or the equivalent to 2.930 μmol/L.

In addition to secondary EGFR mutations, another mechanism of acquired resistance is an “oncogene switch” model. Our groups have recently shown that the acquired amplification of the MET oncogene occurs in ~20% of EGFR mutated patients with acquired resistance to gefitinib or erlotinib (26, 27). MET couples with other ErbB members and activates downstream signals that bypass the inhibited EGFR (27, 47). The in vitro resistance to erlotinib and gefitinib in this model was also in the range of 5 to 10 μmol/L. Dual inhibition of EGFR and MET with TKIs is able to overcome MET amplified EGFR TKI-resistant tumors (27). Of interest, in almost half of the patients with MET amplification, T790M was identified either in the same biopsy specimen or in biopsy specimens from other sites within the patient (26, 27). This indicates that T790M will continue to be the most prevalent form of EGFR TKI resistance. Other oncogenes, such as the insulin-like growth factor-I receptor, may also play a role in resistance to EGFR TKIs in non-EGFR mutated cells (48). Despite a rapidly growing understanding of the molecular mechanisms of acquired resistance to EGFR inhibitors, there is no standard therapy for the expanding number of EGFR mutated tumors that become resistant to gefitinib. Because, in an unselected population of platinum-refractory NSCLC patients, gefitinib was not statistically better than placebo in controlling disease progression (49), the Food and Drug Administration restricted its use for

Table 2. Clinical, pathologic, demographic, and molecular characteristics, response to therapy, PFS, and OS in the studied patients (Cont’d)

<table>
<thead>
<tr>
<th>PFS, gefitinib (mo)</th>
<th>EGFR resequence</th>
<th>MET amplification</th>
<th>Therapy before erlotinib</th>
<th>Response, erlotinib 150 mg/d</th>
<th>PFS, erlotinib (mo)</th>
<th>Survival from gefitinib (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>delL747-S752+T790M</td>
<td>ND</td>
<td>Cetuximab, experimental Raf inhibitor</td>
<td>PD</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>40</td>
<td>L858R+L747S</td>
<td>No</td>
<td>Experimental EGFR inhibitor</td>
<td>PR</td>
<td>6</td>
<td>&gt;62 (alive)*</td>
</tr>
<tr>
<td>26</td>
<td>ND</td>
<td>ND</td>
<td>None</td>
<td>PD</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>14</td>
<td>ND</td>
<td>ND</td>
<td>None</td>
<td>PD</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>16.5</td>
<td>ND</td>
<td>ND</td>
<td>None</td>
<td>SD</td>
<td>3.7</td>
<td>39</td>
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<tr>
<td>12</td>
<td>delL747-751InsP+T790M</td>
<td>No</td>
<td>None</td>
<td>PD</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>1</td>
<td>ND</td>
<td>ND</td>
<td>None</td>
<td>PD</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>ND</td>
<td>ND</td>
<td>None</td>
<td>PD</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>ND</td>
<td>ND</td>
<td>None</td>
<td>PD</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
<td>ND</td>
<td>None</td>
<td>PD</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
<td>ND</td>
<td>None</td>
<td>PD</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>ND</td>
<td>ND</td>
<td>Experimental heat shock protein 90 inhibitor</td>
<td>PD</td>
<td>1</td>
<td>&gt;20 (alive)*</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
<td>ND</td>
<td>None</td>
<td>PD</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>17</td>
<td>delE746-A750+T790M †</td>
<td>ND</td>
<td>None</td>
<td>SD</td>
<td>5</td>
<td>&gt;49 (alive)*</td>
</tr>
<tr>
<td>16</td>
<td>delE746-A750+T790M †</td>
<td>ND</td>
<td>None</td>
<td>PD</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>delE746-A750+T790M †</td>
<td>ND</td>
<td>None</td>
<td>PD</td>
<td>3</td>
<td>&gt;39 (alive)*</td>
</tr>
<tr>
<td>11</td>
<td>delE746-A750+T790M †</td>
<td>ND</td>
<td>None</td>
<td>SD</td>
<td>6</td>
<td>&gt;44 (alive)*</td>
</tr>
<tr>
<td>11</td>
<td>delE746-A750+T790M †</td>
<td>No †</td>
<td>None</td>
<td>PD</td>
<td>2</td>
<td>32</td>
</tr>
</tbody>
</table>

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Fig. 1. Kaplan-Meier curve for PFS of the EGFR mutated patients during gefitinib therapy.
patients previously benefiting from treatment or participating in clinical trials. Nonetheless, in the same phase III trial, the never smoker and Asian group of patients had a clear clinical benefit (49). Gefitinib continues to be widely used in East Asian countries and in EGFR genotyped patients (19, 50). Erlotinib is approved for use in unselected patients after failure of platinum-based therapy (7), and it, like gefitinib, has excellent efficacy in EGFR mutated patients in retrospective and prospective series (12, 17).

One question that remains unanswered is if gefitinib-resistant EGFR mutated patients could benefit from a switch to erlotinib. To address this, we retrospectively analyzed the clinical course of 18 EGFR mutated NSCLC that were treated with gefitinib and, on resistance, erlotinib. The patient characteristics, type of EGFR mutations (almost all had L858R or exon 19 deletions), and initial response to gefitinib 250 mg/d were consistent with previous experience in EGFR mutated patients (17, 19). Our clinical observation was that the majority (>83%) of the gefitinib-resistant patients given erlotinib 150 mg/d had radiographic progression within the first 2 to 4 months of exposure. This is consistent with our preclinical observations, because we expected gefitinib-resistant tumors to predominantly harbor T790M and/or MET amplification, which are cross-resistant to both EGFR TKIs as described above.

We had a second biopsy specimen in 7 of the 18 patients, and in 6 of them, the T790M secondary mutation was identified together with the initial activating exon 19 deletion. None of the 3 patients analyzed had MET amplification (Table 2). Almost all of these gefitinib-resistant patients had rapid progression on erlotinib. Only 1 patient achieved a partial radiographic response on switching to erlotinib (29). This patient had acquired the rare L747S mutation after exposure of the initial L858R-carrying tumor to gefitinib. As reported previously by our group, L858R-L747S is less sensitive to gefitinib and erlotinib than L858R in vitro (28). However, this compound mutation can be inhibited by increasing concentrations of gefitinib or erlotinib at a level that is clinically achievable for the later drug (29). We were not able to measure pharmacokinetic variables of either gefitinib or erlotinib during the course of therapy in this patient; however, the observed skin-related side effects (rash and pruritus) while on erlotinib 150 mg/d exceed in grade the effects while the patient was on gefitinib 250 mg/d (29), likely indicating a higher biologically active dose of the former compound in this individual. However, even in this patient, the duration of response was relatively short and radiographic progression was noted after 6 months. Further biopsies were not available to test if the tumor had acquired additional mechanisms of resistance, such as T790M or MET amplification.

Two recent reports have described the clinical experience of using erlotinib following gefitinib failure in Asian patients. The first was a phase II trial of erlotinib 150 mg/d in patients with either primary or acquired resistance to gefitinib (41). In the initial report, none of the EGFR mutated patients had a radiographic response to erlotinib. All of the EGFR mutated patients from that study were included in our analysis and we report updated clinical data in their response to both gefitinib and erlotinib. The second study evaluated 14 unselected patients that had failed gefitinib, and 5 harbored EGFR mutations (51). Of the EGFR mutated patients, a clinical and radiographic response was described for 2 patients after exposure to erlotinib. However, in 1 of these cases, the patient progressed on erlotinib within the first 2 months of therapy. In the 5 EGFR mutated patients, the time to progression on erlotinib averaged 3 months, whereas the initial time to progression on gefitinib exceed 8 months (51). No molecular data were available for these patients after progression on gefitinib. Anecdotal reports of the use of erlotinib after failure of gefitinib have been published by many investigators (52–57) and recently summarized by one of us (58). Combining all reports and the data presented here by us, it seems that most of the patients that harbored an EGFR mutation, when the genotype was available, did not benefit significantly from erlotinib after they had received and progressed on gefitinib. In almost all patients that harbored an acquired T790M mutation after gefitinib, rapid progression was noted on erlotinib.

However, we cannot exclude the possibility that continued EGFR inhibition, either with the original EGFR TKI or with a different anilinoquinazoline, benefits EGFR mutant patients. The readministration of gefitinib or erlotinib in previously responsive patients that show radiographic progression has been reported to improve symptoms and the clinical course of patients (59, 60), suggesting a role for continued TKI use.

### Table 3. Response and PFS of EGFR mutated gefitinib-resistant patients on erlotinib monotherapy

<table>
<thead>
<tr>
<th>Response</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. patients (%)</td>
<td>1 (6)*</td>
<td>3 (16)</td>
<td>14 (78)</td>
</tr>
<tr>
<td>PFS, mo (95% CI)</td>
<td>2 (2-3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The only patient with PR had the L858R-L747S EFGR mutation, which in vitro is sensitive to achievable serum levels of erlotinib 150 mg/d.

![Fig. 2. Kaplan-Meier curve for PFS of the gefitinib-resistant EGFR mutated patients during erlotinib therapy.](image)
to control the non-TKI-resistant clones of these "oncogene-addicted" cancers. Indeed, in our cohort of patients, we noted that patients with acquired resistance to gefitinib had modestly longer PFS on erlotinib than the ones that had de novo resistance, indicating that perhaps, in EGFR mutated patients with a prior response to TKIs, control of nonresistance clones is achievable and may improve clinical outcomes. Ongoing phase II randomized trials are attempting to confirm if maintaining some form of EGFR TKI therapy in addition to other lines of therapy is better than placebo in EGFR mutated patients with resistance to gefitinib or erlotinib.

Initial steps have begun to use preclinical data for rationale design of clinical trials of patients with acquired resistance to gefitinib or erlotinib. Our groups have shown that some irreversible and second-generation EGFR inhibitors in vitro can partially overcome the T790M mutation (22, 38, 46, 61). This knowledge has spawned phase II trials of the HKI-272 (ClinicalTrials.gov identifier: NCT00266877), BIBW-2992 (ClinicalTrials.gov identifier: NCT00656136), and XL-647 (ClinicalTrials.gov identifier: NCT00522145) compounds in this selected patient population. However, in recent in vitro cell line models and in vivo mouse models, HKI-272 used at doses achieved in the phase I clinical trial (62) actually induced the acquisition of EGFR-T790M (63) or was ineffective generating a radiographic response in L858R-T790M tumors (64). Thus, it is possible that at the achievable clinical concentrations of this, and other novel EGFR inhibitors, T790M will not still be inhibited. Continued development of alternative EGFR inhibitors that have a better profile against EGFR mutated tumors with T790M, such as PF00299804 (65), and development of MET inhibitors may one day help circumvent acquired resistance to EGFR-targeted therapy.

In summary our data indicate that, in EGFR mutated patients with acquired resistance to gefitinib at 250 mg/d, a switch to erlotinib at 150 mg/d does not lead to radiographic responses in most patients despite the higher biologically active dose of erlotinib (36, 37). The PFS was also short in these erlotinib-treated patients with a median of 2 months. These findings were expected, because preclinical models indicated that the two most common mechanisms of acquired resistance to gefitinib, EGFR-T790M and MET amplification, are highly resistant to achievable clinical concentrations of erlotinib (22, 23, 26, 27). As expected from our preclinical models, the only patient that achieved a radiographic response harbored the borderline resistant L858R-L747S mutation, which, similar to L858R-D761Y, can be overcome by increasing concentrations of either gefitinib or erlotinib at 150 mg/d (24, 28, 29).

Disclosure of Potential Conflicts of Interest

D.M. Jackman received consulting fees from Roche and Genentech; G.J. Riely received consulting fees from Boehringer-Ingelheim and Roche; P.A. Jänne has received consulting fees from Roche and AstraZeneca and other remuneration from Genzyme; L.V. Sequist has received consulting fees from Genentech; and W. Pao has not received remuneration from Molecular MD.

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