Selecting Patients for Treatment with Epidermal Growth Factor Tyrosine Kinase Inhibitors

Philip D. Bonomi, Lela Buckingham, and John Coon

Abstract

Identification of objective tumor regressions with epidermal growth factor receptor tyrosine kinases (EGFR TKI) in non–small cell lung cancer (NSCLC) patients has resulted in intense, worldwide clinical and basic research directed toward finding the optimal use of EGFR TKIs in NSCLC. EGFR TKI clinical trials have shown that higher response rates and longer survival are associated with specific patient characteristics and that using conventional chemotherapy simultaneously with EGFR TKIs in unselected patients does not increase survival. Molecular studies have revealed that EGFR-activating mutations and high EGFR gene copy number are frequently found in patients who have the best outcomes with EGFR TKIs. More recent studies suggest that KRAS mutations may identify the subset of patients who have the worst outcome with the EGFR TKI treatment. Currently, investigators are trying to determine the optimal approach to selecting patients for treatment with EGFR TKIs. Studies that have evaluated the potential predictive value of clinical features and/or molecular profiles in EGFR TKI-treated NSCLC patients are discussed in this review.

Preclinical studies with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) suggested that these agents would be cytostatic (1, 2). The observation of significant, often dramatic, tumor regressions induced by EGFR TKIs in heavily pretreated patients with advanced non–small cell lung cancer (NSCLC) was therefore unexpected (3, 4). Since those initial observations, there have been several revealing findings with EGFR TKIs, including discovery of higher response rates in never smokers (5), Asians (6), women (6–9), and patients with adenocarcinomas (7–9). Similarly, the negative results in phase III trials comparing chemotherapy doublets plus an EGFR TKI versus chemotherapy alone (10–13) were particularly disappointing because preclinical observations (14) and theoretical considerations suggested a relatively high chance of success with this strategy.

The observation of higher response rates with EGFR TKIs in selected groups of patients, as well as the disappointing results with simultaneous chemotherapy and EGFR TKIs in unselected patients, led lung cancer researchers to study the potential predictive value of molecular profiles in patients treated with EGFR TKIs. However, negative findings about the predictive value of EGFR protein expression in gefitinib-treated patients raised considerable doubt about the role of molecular profiles in patient selection (15). With the discovery of EGFR-activating mutations in tumors from most patients who had EGFR TKI–induced tumor responses (16, 17), skepticism was soon replaced by enthusiasm for molecular profile research in patients treated with EGFR TKIs. There is increasing evidence that EGFR mutations (18–21) and high EGFR gene copy number (22, 23) are associated with higher response rates and longer survival.

Although clinicians are delighted to have an effective new treatment and new insights about lung cancer biology, they are faced with several questions about the use of EGFR TKIs. Are molecular profiles superior to clinical characteristics in selecting patients for EGFR TKI treatment? Is there an optimal molecular predictor or set of predictors? Are any of the markers sufficiently reproducible and cost effective for clinical use? Because the putative predictors cannot be ordered from most hospital laboratories, how are clinicians to obtain the desired information? Should some stage IV NSCLC patients receive an EGFR TKI as initial therapy? Results of studies evaluating clinical and molecular predictors of EGFR TKI efficacy will be reviewed in this article.

Clinical Predictors of EGFR TKI Efficacy

It seems likely that clinical predictors will continue to be important because 75% of NSCLC patients present with advanced disease, and frequently, their diagnosis is based on scanty cytologic and histologic specimens, which may not be adequate for performance of molecular profiles. Response rates for gefitinib and erlotinib range from 8% to 18% in phase II (4, 6, 7) and phase III single-agent trials (8, 9). Gender has been identified as an indicator of response to EGFR TKIs (6–9). In one trial, gefitinib produced a 19% response rate in women versus 3% in men (P = 0.001; ref. 7). Similar results were observed for symptom relief, with 50% of women experiencing significant symptom relief versus 31% of men (P = 0.06; ref. 7). In another study, the probability of responding to gefitinib was more than 2.5 times higher for women compared with men.
However, it seems equally likely that the discordant results for erlotinib (response rate was 14.7% for women versus 5.1% for men; ref. 9) and gefitinib (response rate was 14.4% for women versus 6.0% for men; ref. 8).

Adenocarcinoma histology and Asian ethnicity were also identified as predictors of higher response to EGFR TKIs in phase II (6, 7) and phase III trials (8, 9). Miller et al. (5) were the first to identify that never smokers had significantly higher response on gefitinib than current or former smokers. In this initial, relatively small, study, the response rate for never smokers was 36% versus 8% for current or former smokers. Larger follow-up studies confirmed significantly higher responses for never smokers compared with current or former smokers treated with either erlotinib (8) or gefitinib (9).

Longer time from completion of previous chemotherapy (≥6 months) and longer time from initial diagnosis to start of erlotinib (≥12 months) were associated with significantly higher response rates in the initial erlotinib study, suggesting that indolent tumors might be more responsive to EGFR TKIs (4). The observation of higher response rates in never smokers also seems to be consistent with this hypothesis because lung tumors arising in never smokers seem to have less genetic instability (24) and, therefore, are possibly less aggressive than tumors that occur in smokers.

The potential relationship between clinical predictors and survival has been evaluated in two phase III trials. Never smoking, Asian ethnicity, and adenocarcinoma histology were associated with significantly longer survival in both studies (8, 9). Time from initial diagnosis to initiation of erlotinib was included in univariate and multivariate analyses in a Canadian trial (BR.21). Patients whose diagnosis was established ≥12 months before starting erlotinib survived significantly longer (23). Results for multivariate analyses evaluating clinical prognostic factors were not reported for the gefitinib phase III study (ISEL; ref. 9).

Significantly longer survival was observed with erlotinib in BR.21 (8), whereas gefitinib was not associated with significantly longer survival in ISEL (9). Patient selection might have been a critical factor in the negative outcome of the ISEL study. Eligibility requirements for both studies were similar, with the exception that eligibility in the ISEL trial was limited to patients whose lung cancer had progressed within 3 months of completion of their most recent chemotherapy. In BR.21, there was no limitation on the interval from completion of last chemotherapy to time of study entry. Patient characteristics for both studies are shown in Table 1. The percentages of patients who were women, never smokers, had adenocarcinoma histology, and had received two previous chemotherapy regimens were quite similar in both studies (8, 9). However, there are relatively large numerical differences in the objective remission rates on previous chemotherapy (40% on BR.21 versus 18% on ISEL; refs. 8, 9). Similarly, there was a higher percentage of patients with a long interval from initial diagnosis to trial entry in BR.21 (≥12 months) compared with ISEL. The number of Asians was higher in the ISEL trial (8, 9).

Potential explanations for the discordant survival results for these studies include the possibility that erlotinib is more effective than gefitinib or that gefitinib dosing was suboptimal. However, it seems equally likely that the discordant results for the erlotinib and gefitinib studies were due to inherent differences in the study populations. The survival hazard ratio (HR) for erlotinib versus placebo showed a greater reduction in the risk of dying for patients who had responded to previous chemotherapy (HR, 0.7; P = 0.004) compared with patients with progressive disease on previous chemotherapy (HR, 0.9; P = 0.34; ref. 8). Multivariate analyses revealed that a longer time interval from diagnosis to study entry in the BR.21 study was significantly related to longer survival. The lower rate of response to previous chemotherapy and the lower percentage of patients who had a longer interval (≥12 months) from diagnosis to study entry in the ISEL study (see Table 1; ref. 9) might have reduced the number of patients who were likely to have a favorable outcome with an EGFR TKI, resulting in negative overall survival results.

Table 1. Patient characteristics in phase III trials comparing erlotinib (BR.21) or gefitinib (ISEL) with placebo

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BR.21 (8), %</th>
<th>ISEL (9), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Never smoker</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>Asian</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Two previous chemotherapy</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete or partial remission</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>on previous chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entered trial ≥12 mo</td>
<td>59</td>
<td>37</td>
</tr>
<tr>
<td>after initial diagnosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EGFR TKI versus Chemotherapy**

There is increasing interest in treating frail elderly or nonambulatory patients with advanced lung cancer with systemic therapy. EGFR TKIs produce rash and/or diarrhea in a relatively large proportion of patients, but there is a general feeling that EGFR TKIs are better tolerated than chemotherapy. Based on this perception, Lilienbaum et al. (25) conducted a randomized phase II trial comparing paclitaxel/carboplatin with erlotinib in previously untreated stage IV NSCLC patients with poor performance status. There were no other specific selection criteria in this study. Approximately 50 patients were treated on each arm, and a trend for longer progression-free and overall survival was observed in patients treated with paclitaxel/carboplatin. In contrast, using clinical features to enrich the study population in a phase II trial of gefitinib in previously untreated stage IV NSCLC patients, Lee et al. (26) observed a 62% response rate and a 1-year survival rate of 77% in 50 Korean women with adenocarcinoma who had never smoked. These collective results suggest that first-line use of EGFR TKIs should be limited to NSCLC patients who have the clinical or molecular profiles associated with the most favorable outcome during EGFR TKI treatment.

Results from randomized trials of second-line single-agent chemotherapy reveal response rates varying from 6.7% to 10.8%, median survival durations ranging from 7 to 8.3 months, and 1-year survival rates of 29.7% to 37.0% (27–30). The results from second- and third-line phase III EGFR TKI studies are similar: response rate of 8.9%, median survival of 5.6 to 6.7 months, and 1-year survival of 27% to 31% (8, 9).
Based on currently available information, it seems that single-agent chemotherapy and erlotinib produce similar results in the second-line setting. A phase III trial comparing gefitinib with docetaxel as second-line/third-line treatment in unselected patients is nearing completion and should provide significant information about potential differences in effectiveness of an EGFR TKI versus single-agent chemotherapy in specific patient groups.

From a clinician’s perspective, grouping patients into best, intermediate, and worst categories with respect to potential benefit from EGFR TKIs has practical implications. Based on currently available information, an example of one of the best groups might include Asian women who had never smoked and have adenocarcinoma. An intermediate group might comprise female smokers with adenocarcinoma, and the worst group might consist of male smokers with squamous cell carcinoma.

Clinicians are also faced with the question of whether EGFR TKI treatment is not worthwhile in specific patient subgroups based on their clinical characteristics. HRs from the Canadian erlotinib study showed that erlotinib was more effective in never smokers (HR, 0.42) than smokers (HR, 0.87), but it is important to note that the risk of death was reduced in smokers and other “less favorable” patient subsets (8). Thus, at this point, it does not seem that patients should be excluded from EGFR TKI treatment based solely on clinical considerations. Perhaps more importantly, we need to gather more information about the benefit of chemotherapy versus EGFR TKIs in specific patient populations. Development of predictive models based on multiple clinical variables might be particularly useful in deciding about chemotherapy versus an EGFR TKI.

**Molecular Predictors of EGFR TKI Efficacy**

EGFR protein expression defined by immunohistochemistry was the first molecular variable evaluated as a potential predictor of EGFR TKI treatment outcome. In the initial report, EGFR expression was determined by immunohistochemistry using a DAKO antibody (14). Tumors having no expression in 90% of the cells were defined as negative. The investigators did EGFR immunohistochemistry in 157 patients treated with gefitinib and found a 15% response rate in patients whose tumors were EGFR negative compared with a 17% response rate in the entire 157-patient cohort. They concluded that EGFR expression determined by immunohistochemistry did not seem to have predictive value for response to gefitinib (15). Subsequently, Cappuzzo et al. (22) evaluated EGFR protein expression using an antibody prepared by Zymed Laboratories. They classified tumor cell EGFR staining intensity on a 0 to 4 scale and calculated the H score by multiplying staining intensity by the percentage of EGFR-positive cells. Defining an H score ≥ 200 as positive, they observed significantly higher response rates, longer time to progression, and longer survival in patients whose tumors had high expression. However, positive EGFR expression was not a significant predictor of survival in their multivariate analyses.

Canadian investigators analyzed EGFR expression using the DAKO anti-EGFR antibody, and they defined tumors as positive for EGFR expression providing ≥10% of cells showed EGFR staining. In univariate analyses, erlotinib was associated with a 30% reduction in the risk of death (P = 0.02) in patients with EGFR-positive tumors compared with a 10% reduction (P = 0.70) in EGFR-negative patients (22). Consistent with results reported by Cappuzzo et al. (22), EGFR expression defined by immunohistochemistry was not significant in their multivariate analyses. Currently, many investigators believe that EGFR protein expression defined by immunohistochemistry is difficult to standardize and is unlikely to play a major role in selecting patients for treatment with EGFR TKI.

In May of 2004, two groups of investigators (16, 17) reported activating mutations in the EGFR tyrosine kinase domain (exons 18, 19, and 21) in tumor specimens from virtually all of their patients who had experienced objective responses on gefitinib. These mutations were absent in tumor specimens from patients with progressive disease. Subsequently, investigators in New York also found EGFR-activating mutations in tumors from patients who were successfully treated with either gefitinib or erlotinib (31). These findings prompted an explosion of basic research in patients treated with EGFR TKIs. The results are summarized in Table 2.

Five groups of investigators have evaluated the potential relationship between progression-free survival and EGFR mutations in patients treated with gefitinib in single-arm studies (Table 2; refs. 18–22). Four single-arm studies (18–21) have shown significantly longer overall survival in patients with EGFR mutations, whereas the remaining single-arm study showed a nonsignificant trend for longer survival associated with EGFR mutations (22). For all the patients with

**Table 2. WT EGFR versus EGFR mutations related to response rate, progression-free survival, and overall survival in patients treated with EGFR TKIs**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Patients (n)</th>
<th>% Mutation (%)</th>
<th>Response rates</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>WT/mutation (%)</td>
<td>WT/mutation (mo)</td>
<td>WT/mutation (mo)</td>
</tr>
<tr>
<td>Cappuzzo (22)</td>
<td>89</td>
<td>19</td>
<td>5 vs 53</td>
<td>&lt;0.001</td>
<td>2.6/9.9</td>
</tr>
<tr>
<td>Cortez-Funes (18)</td>
<td>83</td>
<td>12</td>
<td>9 vs 60</td>
<td>&lt;0.001</td>
<td>3.6/12.3</td>
</tr>
<tr>
<td>Han (19)</td>
<td>90</td>
<td>19</td>
<td>14 vs 65</td>
<td>&lt;0.001</td>
<td>1.8/21.7</td>
</tr>
<tr>
<td>Mitsudomi (20)</td>
<td>59</td>
<td>56</td>
<td>10 vs 84</td>
<td>&lt;0.0001</td>
<td>NA</td>
</tr>
<tr>
<td>Takano (21)</td>
<td>66</td>
<td>59</td>
<td>11 vs 82</td>
<td>0.005</td>
<td>1.7/12.6</td>
</tr>
<tr>
<td>Tsao* (23)</td>
<td>100</td>
<td>37</td>
<td>7 vs 16</td>
<td>0.37</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: PFS, progression-free survival; OS, overall survival; NA, not available.
* Fifty percent of patients had mutations in exons 18, 19, and 21. Remaining patients had mutations in other exons.
mutations (n = 110) in Table 2 combined, the response rate is 60%. EGFR mutations were not significantly related to survival in the Canadian trial comparing erlotinib with placebo (18), and these investigators have pointed out the possibility that EGFR mutations may simply be a prognostic factor rather than a predictive factor for EGFR TKI efficacy (32). In their trial, survival was longer in patients with classic mutations compared with novel mutations or wild-type (WT) EGFR in the placebo arm. In addition, survival HRs for patients treated with erlotinib compared with placebo were quite similar in patients with classic mutations (0.65), versus novel mutations (0.67), versus WT EGFR (0.73; ref. 32). Subsequently, Italian investigators (33) have provided evidence that the novel EGFR mutations observed by Tsao et al. (32) most likely were artifacts.

Similarly, results from a phase III trial revealed no significant survival difference in the subset of patients with EGFR mutations treated with either chemotherapy alone or chemotherapy plus erlotinib (34). In the same trial, another subgroup analysis, which evaluated survival for mutant versus WT EGFR in patients treated on the chemotherapy-alone arm, revealed significantly longer survival in patients with EGFR mutations (34). Although the subset analyses included relatively small numbers of patients, these provocative results indicate that additional information is needed to sort out the predictive versus the prognostic implications of EGFR mutations (32). The majority of EGFR mutations occur in exons 19 and 21. Recent information suggests that response rates are higher in patients with exon 19 mutations than those with exon 21 mutations, and longer survival has been associated with exon 19 mutations in at least two of these studies. Results from these studies are summarized in Table 3 (20, 35–38).

EGFR gene copy number has also been evaluated as a potential predictor of EGFR TKI. Cappuzzo et al. (22) has studied EGFR copy number in 100 patients treated with gefitinib. They developed a definition for high EGFR gene copy number based on one or more of the following conditions being met: ≥40% of cells contain ≥4 copies of the EGFR gene; the average EGFR copy number in all cells is ≥2; or 10% of cells contain ≥15 EGFR genes per chromosome. Using this definition to classify tumors as positive by fluorescence in situ hybridization (FISH), these investigators observed significantly higher response rates, longer time to progression, and superior overall survival in univariate analyses, and, more importantly, FISH positivity was significantly associated with longer survival in multivariate analyses (22).

Tsao et al. (23) applied the same definition for FISH positivity in a patient subset (n = 125) treated with either erlotinib or placebo in their phase III trial. They observed significantly higher response rates (HR for survival, 0.44; P = 0.008) for erlotinib versus placebo in the FISH-positive group. Despite the relatively large reduction in the risk of death in their univariate analysis, FISH positivity was not significantly related to survival in a multivariate analysis. Only the following clinical variables were associated with significantly longer survival in their multivariate analyses: treatment with erlotinib, ambulatory performance status, never smoking, Asian ethnicity, weight loss < 5% of usual body weight, and interval between diagnosis and trial entry (≥ 12 months; ref. 23).

Recent reports suggest that KRAS mutations are associated with low response rates in patients treated with EGFR TKIs. Miller et al. (39) found KRAS mutations in 9 of 38 patients whose tumors were refractory to treatment with an EGFR TKI. In contrast, no KRAS mutations were found in 21 patients in whom EGFR TKIs produced favorable tumor responses. Subsequently, this group of investigators reported a 32% response rate with EGFR TKIs in patients whose tumors contained WT KRAS compared with no responses in patients with KRAS mutations (P = 0.01; ref. 40). They also observed a trend for longer survival with WT versus mutant KRAS, with median survival times of 21 versus 13 months, respectively (P = 0.24; ref. 41). Perhaps, the most interesting observations about KRAS mutations have been reported by Eberhard et al. (34) and Tsao et al. (41) who observed a potential detrimental effect of erlotinib in patients with the mutations. Eberhard et al. (34) noted significantly shorter survival in 25 patients with KRAS mutations treated with chemotherapy plus erlotinib compared with 30 patients with KRAS mutations treated with chemotherapy alone. Similarly, Tsao et al. (41) observed a higher risk of dying associated with erlotinib compared with placebo in 30 patients with KRAS mutations (HR, 1.67; P = 0.31). Although these results are provocative, additional data are needed to sort out the predictive value of KRAS mutations in patients treated with EGFR TKIs.

At the time of acquired EGFR TKI resistance in tumors with activating mutations, novel EGFR point mutations (T790M) are found in ~50% of the tumors (42). In addition, exogenous introduction of EGFR T790M into gefitinib-sensitive malignant cells with EGFR-activating mutations or gene amplification results in resistance to EGFR TKIs (43). There is also evidence that EGFR exon 20 insertions confer resistance to EGFR TKIs (44).

Investigators at Vanderbilt University and the University of Colorado have taken a novel approach in trying to identify molecular markers predictive of EGFR TKI efficacy (45). They are using mass spectroscopy to evaluate serum protein patterns and have identified proteins associated with relatively long versus relatively short survival in patients treated with an EGFR TKI. Their finding that longer survival was observed in patients who had “good” serum patterns despite less favorable clinical characteristics (e.g., smoking and squamous carcinoma) is particularly interesting. Although additional data are needed, their preliminary results and the ease of obtaining serum in patients with advanced lung cancer make serum proteomics an attractive methodology.

### Practical Implications of Molecular Profiles

From a clinician’s perspective, it would be useful to categorize patients into the best, intermediate, and worst EGFR TKI response groups.
EGFR TKIs have provided an important alternative approach for palliation of previously treated advanced disease NSCLC patients, and it is likely that there will be increasing use of first-line EGFR TKIs in subgroups of NSCLC patients based on their clinical and molecular characteristics. Perhaps most importantly, testing EGFR TKIs in early-stage NSCLC populations, which have been enriched on a clinical or molecular basis, might result in significant improvement in long-term survival for lung cancer patients, analogous to the results with trastuzumab in early-stage breast cancer patients whose tumors showed increased Her2 expression/gene amplification (47). Determining the optimum way to select patients for future EGFR TKI studies seems to be a key factor in improving results for individual lung cancer patients.

### Open Discussion

**Dr. Thomas Lynch:** Dr. Davies, I will start off by asking you what you think copy number is telling us. Why does having a couple of extra copies of the chromosome matter, as opposed to gene amplification? How does that mechanistically explain what is going on?

**Dr. Angela Davies:** I think we are still learning what that means. It highlights the fact that mutations don’t tell the whole story. The patients with mutations are the ones who are going to have dramatic and durable responses to these agents. There is another population of patients who do not benefit and that may partly be predicted by the presence of KRAS mutations. It is that large middle group of patients who would benefit from EGFR inhibitors that we are struggling to identify and select. That may be where the gene copy number fits in terms of predicting when to utilize these agents.

**Dr. Charles Butts:** There are very few predictors to say you shouldn’t treat a particular population with erlotinib. As Dr. Bonomi has shown, the hazard ratios are fairly consistent until you get to the male smoker with squamous carcinoma, where it is 0.91. Otherwise, the clinical predictor factors would not select against giving someone erlotinib as second-line therapy.

**Dr. Bruce Johnson:** Both of these compounds, gefitinib and erlotinib, were developed against wild-type epidermal growth factor receptor. So far, the data are consistent with the hypothesis that gefitinib may work better in mutants. The data are also consistent with erlotinib being more active against the wild-type receptor, which may explain some of the differences observed between BR.21, which used erlotinib, versus most of the Japanese studies, which have used gefitinib. We should look to see if other drugs are more active against mutants than what we have now.

### Table 4. EGFR TKI response rate in NSCLC

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Treatment</th>
<th>CR/PR (%)</th>
<th>Stable (%)</th>
<th>Disease control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kris (7)</td>
<td>Gefitinib</td>
<td>11</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Fukuoka* (6)</td>
<td>Gefitinib</td>
<td>18</td>
<td>34</td>
<td>52</td>
</tr>
<tr>
<td>Perez-Soler (4)</td>
<td>Erlotinib</td>
<td>12</td>
<td>35</td>
<td>47</td>
</tr>
<tr>
<td>Shepherd (8)</td>
<td>Erlotinib</td>
<td>9</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>Thatcher (9)</td>
<td>Gefitinib</td>
<td>8</td>
<td>32</td>
<td>40</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; PR, partial remission.

*Relatively high proportion Asian population.

### Table 5. Frequency of EGFR mutations, high EGFR gene copy number, and KRAS mutations in NSCLC

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Patients (n)</th>
<th>EGFR mutation (%)</th>
<th>EGFR FISH positivity (%)</th>
<th>KRAS mutation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shigematsu (45)</td>
<td>617</td>
<td>21</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>Tom* (46)</td>
<td>215</td>
<td>53</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>Cappuzzo (22)</td>
<td>102</td>
<td>17</td>
<td>45</td>
<td>—</td>
</tr>
<tr>
<td>Tsao (23)</td>
<td>125</td>
<td>12</td>
<td>—</td>
<td>15</td>
</tr>
<tr>
<td>Tsao (41)</td>
<td>206</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Predominantly Asian population.
**Dr. Jeffrey Engelman:** For the patients who are having these remarkable responses, it is more a question of oncogene addiction. These are cancers relying on EGFR receptor to activate the critical downstream signaling pathways. The mutations and amplifications are just telling you that those are the cancers that are driven by EGFR. In the Cappuzzo study (22), mutations and amplifications were statistically significantly associated with one another. If you look at a Venn diagram, it is a huge overlap. In the preclinical models, the cell lines that have mutations and are markedly sensitive, they are all amplified, so it is just part of the oncogene addiction.

**Dr. Gregory Riely:** We know that EGFR mutation—positive patients benefit greatly from erlotinib. The second point that we really emphasize is that patients with KRAS mutations do not benefit. However, it is important to remember that very few EGFR mutation tests are done in the real world, but even fewer KRAS tests are done.

**Dr. Lynch:** We now have studies that show that selecting patients by mutation status is associated with a very good response to treatment. We don’t know yet whether this is a prognostic or a predictive factor. Where do you stand on the mutation versus KRAS versus IHC versus copy number debate?

**Dr. Roy Herbst:** We have looked at our data, and the KRAS story holds pretty true in the M. D. Anderson database. The mutation is actually a strong negative predictor. The FISH data in the Anderson experience do not hold up as well. My sense is it is going to be a combination of these different markers that will ultimately be used.

**Dr. Leena Sequist:** As a practical point, in doing our first-line mutation study with gefitinib, we have learned how difficult it can be to molecularly profile people when they are first diagnosed with advanced stage non–small cell lung cancer. Getting the proper amount of tissue and being able to process it in a timeframe that fits into the decision-making with the patient is no easy feat. Not just with these markers and these two drugs, but with other molecularly targeted agents down the road, we need to shift our paradigm of how we diagnose people and how we can do these tests in a reasonable timeframe.

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**References**


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