Targeted Therapy for the Treatment of Advanced Non-small Cell Lung Cancer*

A Review of the Epidermal Growth Factor Receptor Antagonists

Gerard A. Silvestri, MD, FCCP; and M. Patricia Rivera, MD, FCCP

Lung cancer is the most common cause of cancer death. The vast majority of patients present with non-small cell lung cancer (NSCLC) in advanced inoperable stages. The current first-line treatment for patients with advanced NSCLC includes chemotherapy and palliative radiotherapy, but most patients relapse and eventually succumb to the disease. Advances in our knowledge of cancer cell biology have led to the development of specific molecular-targeted therapeutic agents. Mutations in the epidermal growth factor receptor (EGFR) have been identified in NSCLC cells, and overexpression of the EGFR and its ligands is a common feature of many cancers; therefore, EGFR has become an attractive target for various antitumor strategies. Aberrant signaling from the EGFR is known to be important in the development and progression of NSCLC. Two oral EGFR inhibitors, gefitinib and erlotinib, are small-molecule agents that selectively inhibit the intracellular tyrosine kinase activity of the EGFR. Both have demonstrated antitumor activity in patients with advanced NSCLC who have failed all prior treatment regimens. In addition, the anti-EGFR monoclonal antibody cetuximab has shown promising activity in both first-line and second-line settings in patients with advanced NSCLC. Furthermore, patients with severe comorbidities who would not be eligible for systemic chemotherapy are candidates for these targeted therapies. Finally, these agents have also been shown to be effective for relieving symptoms, maintaining stable disease, and improving quality of life without the adverse events that may be associated with cytotoxic cancer therapies. This report will review the mechanism of action, indications, contraindications, patient selection, and efficacy and side effects of this new class of compounds. It is important for pulmonologists to be aware of this class of compounds, as they can provide benefit to patients with NSCLC who may not have been previously considered for antitumor therapy.

Key words: epidermal growth factor receptor; lung cancer; targeted therapy; tyrosine kinase inhibitor

Abbreviations: EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; FDA = Food and Drug Administration; IDEAL = IRESSA Dose Evaluation in Advanced Lung Cancer; ILD = interstitial lung disease; NSCLC = non-small cell lung cancer; PS = performance status; TGF = transforming growth factor; TK = tyrosine kinase; TKI = tyrosine kinase inhibitor

Lung cancer is one of the most commonly occurring malignancies, second to prostate cancer among men and breast cancer among women. However, lung cancer has the highest mortality rate for all cancers among both men and women, accounting for almost one third of all cancer deaths. Although lung cancer mortality among men decreased an average of 1.6% per year from 1990 to 2000, the mortality of lung cancer in men still surpasses that of prostate cancer and colorectal cancer. A frightening increase in lung cancer mortality in women occurred from 1950 to 2000, and currently lung cancer kills more women each year than breast, uterine, and ovarian cancers combined. Lung cancer remains a disease with a high fatality rate (5-year survival rate of 15% from 1989 to 1994).

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. The majority of patients with NSCLC present with locally advanced inoperable or metastatic disease. The prog-
nosis is especially poor for patients with advanced NSCLC who have not responded to multiple prior chemotherapy regimens. The goals of therapy for advanced lung cancer include symptom improvement, disease stabilization, and improved quality of life.

**Current Treatment Strategies for the Management of NSCLC**

The management of NSCLC largely depends on the stage of disease at diagnosis. The current first-line therapeutic option for patients with advanced NSCLC includes chemotherapy with a platinum (cisplatin or carboplatin) in combination with a third-generation agent (paclitaxel, gemcitabine, vinorelbine, irinotecan) or nonplatinum agents such as docetaxel. Docetaxel is considered the standard of care as second-line therapy for those who fail to respond to or are adversely affected by platinum-based therapy. The use of cytotoxic chemotherapies has resulted in improvements in both median overall survival and 1-year survival rates compared with best supportive care. Until recently, no clear standard of treatment beyond second-line docetaxel therapy existed for patients with NSCLC who failed to respond or showed no improvement in subsequent cycles of chemotherapy. Patients with advanced NSCLC unresponsive to chemotherapy usually receive palliative radiation to alleviate symptoms by decreasing tumor size and best supportive care for pain control, psychosocial support, and end-of-life care.

A recent, large, randomized, phase III trial compared the efficacy of pemetrexed, a multitargeted antifolate chemotherapy agent, vs docetaxel in patients with advanced NSCLC previously treated with chemotherapy. Pemetrexed resulted in clinically equivalent efficacy outcomes but had significantly fewer side effects compared with docetaxel. As a result of this study, pemetrexed was approved by the US Food and Drug Administration (FDA) for use in recurrent NSCLC.

**Epidermal Growth Factor Receptor as a Target for NSCLC**

Advances in the understanding of tumor biology have led to the identification of many of the key molecular pathways that drive tumor growth. One such pathway is triggered by activation of the epidermal growth factor receptor (EGFR) [Figure 1]. EGFR is a transmembrane glycoprotein belonging to the human EGFR family. It consists of an extracellular ligand-binding domain, a transmembrane region, and a cytoplasmic domain that contains a tyrosine kinase (TK) region. TKs are ubiquitously expressed proteins that are involved in numerous intracellular signaling pathways, including both normal and aberrant cell growth. Both epidermal growth factor (EGF) and transforming growth factor (TGF)-α bind to the EGFR to elicit its biological and mitogenic effects. Ligand binding to the EGFR induces receptor dimerization and activation of the TK activity of the receptor (Fig 1). This step subsequently causes receptor autophosphorylation, initiating signal transduction pathways that lead to cell proliferation, inhibition of apoptosis, and angiogenesis. Dysregulation of these pathways can result in oncogenesis and cancer progression.

There is compelling evidence for a direct link between the EGFR and human cancers. In fact, aberrant TK activity is a hallmark of malignant cells. Many tumors, particularly NSCLC, have increased or altered expression of EGFR-TK or its ligands. Overexpression of EGFR is reported to occur in 40 to 80% of NSCLC cases and is most commonly reported in squamous cell (84%), followed by large cell (65%) and adenocarcinoma (65%). Several studies have indicated that the level of EGFR expression correlates with poor disease prognosis and reduced survival.

The approach of treating NSCLC by inhibiting EGFR signaling is inherently different from commonly used cytotoxic chemotherapies. Whereas chemotherapeutic drugs affect all dividing cells, agents that target the EGFR act selectively on malignant cells due to the limited role of the EGFR in normal nonembryonic tissue. These agents therefore have the potential for considerably reduced toxicity compared with nonspecific cytotoxic agents.

**Novel Agents Target the EGFR**

There are two general approaches for inhibiting EGFR signaling: one is to prevent ligand binding to the extracellular domain with a monoclonal antibody, and the other is to inhibit the intracellular TK activity.

**EGFR-Targeted Antibodies: Mechanism of Action**

The high levels of EGFR expression in NSCLC tumors provide a rationale to investigate EGFR-targeted antibodies. Monoclonal antibodies have been developed to specifically target the extracellular component of the EGFR receptor. They compete...
with TGF-α, EGF, and other natural ligands for EGFR extracellular binding sites thus preventing autophosphorylation of the intracellular region. As a result, the TK domain remains inactive and downstream signaling does not occur, which leads to inhibition of cell cycle progression, promotion of apoptosis, and antiangiogenesis. The chimeric human-murine IgG antibody cetuximab is currently approved for treatment of colorectal carcinoma. Panitumumab (human IgG2) and EDM-72000 (humanized IgG1) are antibodies in earlier stages of development. These antibodies have a prolonged half-life, which allows for weekly or less frequent dosing.

Efficacy of EGFR-Targeted Antibodies in Patients With Advanced NSCLC

Phase I studies of cetuximab demonstrate that this monoclonal antibody has antitumor activity against a variety of solid tumors, including NSCLC, and that it can be safely combined with cisplatin and radiotherapy. In a recent phase III international trial, 424 patients with locoregionally advanced squamous cell cancer of the head and neck were randomized to receive either radiation alone (to a dose of 70 Gy) or radiation plus weekly cetuximab (400 mg/m²). The addition of cetuximab to high-dose radiation resulted in a statistically significant improvement in survival (median survival and 3-year survival in the group treated with cetuximab compared to the radiation-only group were 54 months vs 28 months and 57% vs 44% respectively; p = 0.02). Although additional toxicity was attributed to the cetuximab (patients on the cetuximab study arm were more likely to experience fever, chills, nausea, and emesis), the clinical benefit seen in the cetuximab-plus-radiotherapy group was achieved with minimal enhancement in overall toxicity. A phase II study in chemonaive patients with advanced NSCLC examined the activity of cetuximab added to a standard regimen of cisplatin and vinorelbine. Patients were randomized to receive either cetuximab/cisplatin/vinorelbine (n = 43) or cisplatin/vinorelbine (n = 43). Patients
in the chemotherapy-only study arm had a lower overall response rate (20% vs 31.7%) than those treated with chemotherapy plus cetuximab, suggesting that adding cetuximab may improve the efficacy of cisplatin/vinorelbine in first-line treatment of NSCLC.22 The safety profile in both treatment arms was tolerable, with leukopenia being the most common reported toxicity. A phase II trial by Kim and colleagues23 evaluated the efficacy of cetuximab combined with docetaxel in patients with EGFR-expressing NSCLC who had progressed or had recurrence of disease within 3 months following first-line chemotherapy. In 47 evaluable patients, 13 patients had a partial response and 8 patients achieved stable disease. The regimen was well tolerated, with acneiform rash and neutropenia being the most common toxicities. The authors23 concluded that the combination of cetuximab and docetaxel was a safe and active second-line regimen in patients with NSCLC. To date there are no phase III trial data available on cetuximab in NSCLC, and the drug is not FDA approved for treatment in lung cancer.

**TK Inhibitors: Mechanism of Action**

Inhibitors of TK phosphorylation (TK inhibitors [TKIs]) are small-molecule agents that block EGFR triphosphate-binding site on the intracellular region of the receptor.24 A variety of TKIs have been developed for advanced NSCLC. Gefitinib was the first of the class of EGFR-TKIs to be approved by the FDA for treatment in patients with advanced NSCLC. Gefitinib has been shown to induce radiographic tumor responses, improve symptoms, and improve quality of life in those patients who have failed to respond to previous cancer therapies.25,26 In addition, in the compassionate-use program for gefitinib, which enrolled > 21,000 patients with NSCLC in the United States, the 1-year survival rate was 30%, which is comparable to that of single-agent chemotherapy.27 Several other small-molecule reversible TKIs, including erlotinib, are also being investigated in clinical trials for patients with end-stage NSCLC. Erlotinib has proven efficacy as a second-line or third-line treatment for patients with advanced NSCLC. In a recent phase III trial,28 erlotinib treatment increased survival, decreased symptoms, and improved the overall quality of life in patients with advanced NSCLC compared with placebo. Erlotinib has recently been approved by the FDA as a second-line agent for use in patients with advanced NSCLC.

### Efficacy of EGFR-TKIs in Patients With Advanced NSCLC

**Gefitinib**

Once-daily oral administration of gefitinib has been investigated as monotherapy for advanced, previously treated NSCLC in two non-placebo controlled trials: the first and second IRESSA Dose Evaluation in Advanced Lung Cancer (IDEAL) trials.25,26 In the IDEAL trials, patients were randomized to receive either 250 mg/d or 500 mg/d of gefitinib. Patients in IDEAL-1 (n = 210) had previously received one or two chemotherapy regimens; whereas in IDEAL-2, patients (n = 216) had received two or more prior chemotherapies.25,26 In IDEAL-2, objective tumor response and symptom improvement were the primary end points, and all patients were required to be symptomatic at baseline. IDEAL-1 contained a subset of patients with symptoms at baseline, and safety and efficacy were the primary end points. In both trials, symptom improvement was assessed by the lung cancer subscale of the Functional Assessment of Cancer Therapy-Lung study quality-of-life questionnaire. Symptoms assessed by the lung cancer subscale include shortness of breath, weight loss, clear thinking, cough, appetite, tightness in chest, and ease of breathing.29

Results from the IDEAL-1 and IDEAL-2 trials are summarized in Table 1.25,26 Objective tumor responses with 250 mg/d of gefitinib were observed in 18% of patients in the IDEAL-1 trial and 12% of patients in the IDEAL-2 trial. In each trial, response rates in the 500 mg/d groups were similar to those in the 250 mg/d group.25,26 Radiographic tumor responses were rapid and long lasting in both trials. In the IDEAL-1 trial,25 68% of responses were seen within 1 month after randomization. In the IDEAL-2 trial,26 the median duration of response for patients receiving 250 mg/d or 500 mg/d doses was 7 months and 6 months, respectively. Responses were observed regardless of the number of prior therapy regimens, age, gender, or performance status (PS). Disease control (consisting of objective response plus stable disease) was achieved in approximately 50% of patients in both trials.

Interestingly, in the IDEAL-2 trial,26 objective tumor responses to gefitinib occurred more frequently in women than in men, were higher with adenocarcinoma than other histologic types, and were higher in those patients who had never smoked. The reasons for these differences are presently unknown, but there is likely to be a biological basis for the differential responses in subpopulations of patients with advanced NSCLC. One popular explanation for the rate of response being higher in...
women with adenocarcinoma who have never smoked is that this population is believed to be enriched for EGFR mutations. However, responses to gefitinib have been observed in patients with NSCLC regardless of tumor histologic type or patient demographics.26

In the IDEAL-2 trial,26 symptom improvement for patients receiving 250 mg/d or 500 mg/d of gefitinib was observed in 43% and 35% of patients, respectively (Fig 2). Similar rates of symptom improvement were seen in the IDEAL-1 trial25 among those patients who were asymptomatic at baseline. Among patients who had palliation of symptoms in the IDEAL-2 trial,26 56% had symptom improvement in the first week of treatment and 75% had improvements by 3 weeks (Fig 3). Importantly, in both trials, symptoms improved in 96% of the patients with radiographic tumor responses.26,30,31 Symptom improvement was also strongly correlated with survival and thus could potentially be used as a marker for response (Fig 4).26,30,31 In the IDEAL-2 trial,26 patients with symptom improvement had a median survival of 13 months, whereas the median survival time was 5 months in patients without symptom improvement.

Tumor responsiveness to gefitinib has not been found to be associated with the expression level of EGFR.32,33 Rather, it may be linked to genetic differences in the EGFR of different subpopulations or the level of EGFR-TK activity. Two recent reports have identified specific mutant versions of EGFR in NSCLC cells that seem to determine response to treatment with gefitinib34,35 and with erlotinib.36 These gain-of-function somatic mutations (either small-in-frame deletions or amino acid substitutions) are close in sequence to the catalytic site of the TK domain and result in increased EGF-induced activation and gefitinib-induced TK inhibition34. The addition of the ligand EGF doubled or tripled the activation of the mutant EGF receptors, as compared with the activation of the wild-type EGFR. In addition, while activation of the wild-type EGFR was down-regulated after 15 min, the mutant receptors demonstrated continued activation for up to 3 h.34 The mutations probably stabilize the interaction between gefitinib and the TK, thereby enhancing the inhibitory effect of the drug.34 The mutant receptors bearing these changes are about 10-fold more sensitive to inhibition by gefitinib than

<table>
<thead>
<tr>
<th>Variables</th>
<th>Gefitinib, IDEAL-1 (n = 210)</th>
<th>Gefitinib, IDEAL-2 (n = 216)</th>
<th>Erlotinib (n = 57), 150 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>104 106</td>
<td>102 114</td>
<td>57</td>
</tr>
<tr>
<td>Objective response, %</td>
<td>18.4 19.0</td>
<td>11.8 8.8</td>
<td>13</td>
</tr>
<tr>
<td>Disease control rate (objective response and stable disease), %</td>
<td>54.4 51.4</td>
<td>42 36</td>
<td>51</td>
</tr>
<tr>
<td>Median survival, mo</td>
<td>7.6 8</td>
<td>7 6</td>
<td>ND</td>
</tr>
<tr>
<td>1-yr survival, %</td>
<td>3 3</td>
<td>27 24</td>
<td>ND</td>
</tr>
<tr>
<td>Symptom improvement, %</td>
<td>40 37</td>
<td>43 35</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Data are from the IDEAL trials.25,26,36 ND = not determined.

Table 1—Efficacy Results From Monotherapy Phase II Trials of EGFR-TKIs*

Figure 2. Rates of symptom improvement in the IDEAL trials.25,26

Figure 3. Rate of symptom improvement from onset of medication for patients who experienced improvement in the IDEAL-2 trial.26
wild-type EGFR.\textsuperscript{34} In the study by Lynch et al,\textsuperscript{34} EGFR mutations were found in eight of nine patients with gefitinib-responsive lung cancer, as compared with none of the seven patients who had not responded to the drug ($p = <0.001$). As a group, the nine patients who responded to gefitinib derived substantial benefit from the therapy, with a median duration of survival of $>18$ months from the start of the drug treatment. As noted in previous trials,\textsuperscript{25,26} most patients in the study by Lynch et al\textsuperscript{34} who responded to gefitinib were women, had never smoked, and had bronchioloalveolar tumors. To date, these mutations have only been found in NSCLC cells. It is not yet known whether response to erlotinib also correlates with these mutations. Although mutation may identify those patients who are most likely to have a complete response, it does not exclude other patients from receiving a meaningful clinical benefit from gefinitib.

**Erlotinib**

Erlotinib was investigated in advanced NSCLC in a non–placebo-controlled phase II trial\textsuperscript{37} involving 57 patients who had received at least one round of platinum-based chemotherapy (Table 1). Patients were also required to have EGFR-positive tumors based on immunohistochemistry. The primary outcome was objective tumor response, and secondary outcomes included time to progression, safety, survival, and quality of life. The patients received erlotinib, 150 mg qd. The objective response rate in this trial was 13%, and the rate of disease control was 51%. Among patients who had received two or more chemotherapy regimens ($n = 47$), the response rate was 13%; among patients who had received both a platinum and taxane-containing regimen ($n = 40$), the response rate was 10%.\textsuperscript{37}

Erlotinib was also investigated in a recently completed, placebo-controlled, phase III trial (the BR.21 trial).\textsuperscript{28} Patients were required to have had one or two previous chemotherapy regimens and were randomized 2:1 to receive 150 mg/d of erlotinib or placebo. The primary end point was survival. The response rate was 9% in the erlotinib study arm ($n = 427$) and $<1\%$ in the placebo study arm ($n = 211$). Stable disease was observed in $35\%$ of patients receiving erlotinib and $27\%$ of patients in the placebo group. Survival, both overall (6.7 months, $p = 0.001$) and progression-free (2.2 months, $p < 0.001$) were significantly improved in the erlotinib study arm compared with placebo (Table 2).\textsuperscript{28} Erlotinib also showed significant improvements in symptoms (pain, dyspnea, cough, fatigue) and quality of life compared with placebo.\textsuperscript{28} The results from these trials\textsuperscript{25,26,28,30,31} have collectively demonstrated that inhibiting EGFR-TK activity with either gefitinib or erlotinib in patients with advanced NSCLC can result in radiographic tumor improvement, symptom improvement, and an overall improved quality of life with mild adverse effects.

**Table 2—Survival Results From the BR.21 Trial of Erlotinib vs Placebo**

<table>
<thead>
<tr>
<th>End Points</th>
<th>Erlotinib ($n = 488$)</th>
<th>Placebo ($n = 243$)</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival, mo</td>
<td>2.2</td>
<td>1.8</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Overall survival, mo</td>
<td>6.7</td>
<td>4.7</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>1-yr survival, %</td>
<td>31</td>
<td>22</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Data are from Shepherd et al.\textsuperscript{28} NA = not applicable.
Toxicity of Anti-EGFR Therapy

Skin rash is the most common adverse effect associated with anti-EGFR antibodies. Two histologic patterns of rash have been identified: a superficial dermal inflammatory cell infiltrate surrounding hyperkeratotic infundibula, and suppurative, superficial folliculitis. Trends toward a dose-dependent incidence of the rash have been reported with anti-EGFR antibodies; however the severity of the rash may not be dose dependent. Clinical data suggest a potential relationship between skin rash development and treatment outcomes in patients receiving cetuximab. A review of four phase II studies across multiple tumor types revealed that patients who have a rash after receiving cetuximab have longer survival rates than patients who do not have a rash. In addition, those patients who had a higher-grade skin rash had greater survival rates than those with a less-severe rash.

EGFR-TKIs as a class are generally well tolerated. The two most common toxicities include dermatologic (acneiform rash and dry skin) and GI (diarrhea) side effects. These effects are typically mild to moderate, easily managed, and reversible. With gefitinib, the frequency of drug-related adverse events was dose dependent, with more frequent side effects occurring in patients receiving 500 mg/d compared with those receiving 250 mg/d. There is no evidence that the toxicity of gefitinib is cumulative with successive cycles of treatment.

The acneiform rash is not an allergic reaction but rather appears to be a mechanistic effect of EGFR inhibition in the skin. The correlation between skin rash and clinical benefit of TKIs is under investigation. Conflicting evidence has been seen in clinical trials of gefitinib and erlotinib in advanced NSCLC. In the IDEAL-2 study, the presence of skin toxicities did not correlate with tumor response to gefitinib and was not a marker for antitumor activity.

In postmarketing use in Japan, interstitial lung disease (ILD) has emerged as a rare but serious complication of gefitinib use. Worldwide, the rate of ILD associated with gefitinib in compassionate-use programs or postmarketing use is < 1%, and the mortality rate is approximately 0.3%. In phase III trials comparing standard chemotherapy doublets with or without gefitinib, the rates of ILD were lower and were not significantly different from placebo. In the BR.21 study of erlotinib, ILD was also observed at an incidence of < 1%, which was not significantly different from placebo. It should be noted that standard treatments for lung cancer such as chemotherapy and radiotherapy have an associated incidence of ILD of approximately 1%. ILD should be considered in any patient receiving treatment for lung cancer who has new-onset or worsening dyspnea or has unexplained new infiltrates on radiography, and chemotherapy drugs including the EGFR-TKIs should be discontinued while the appropriate clinical workup is conducted. Acute pneumonia can resolve with discontinuation of therapy with or without a short course of corticosteroids. However, once fibrosis has occurred, there may be irreversible loss of lung function, and a mortality rate of up to 50% in this patient subgroup can be expected.

Patient Selection

There are several patient populations who should be considered for therapy with the oral targeted agents. Currently, the EGFR-TKIs should be considered for patients with advanced or metastatic NSCLC who are refractory to first-line chemotherapy (platinum-based doublet) and second-line chemotherapy (docetaxel or pemetrexed). In addition, these targeted agents offer a new therapy option for patients with advanced NSCLC who have a poor PS, or those who are chemotherapy intolerant. Patients with a poor PS may be unable to tolerate standard chemotherapy regimens. Moreover, evidence suggests that patients with advanced NSCLC and a poor PS receive little benefit from cisplatin-containing chemotherapy. Therefore, the treatment options for these patients are limited and include single-agent chemotherapy or best supportive care. The primary goals of therapy for these patient subsets include palliation of symptoms, disease control, and quality of life. EGFR-targeted agents may offer a new therapy option for patients with a poor PS. These agents have generally mild and well-tolerated side effects without the serious systemic effects of cytotoxic therapies. In addition, EGFR-TKIs are associated with symptom relief and stable disease. Gefitinib has shown good tolerability and some activity in elderly and unfit patients in the compassionate-use setting.

In a phase II trial, gefitinib has also shown promise for use in combination with docetaxel in previously untreated elderly (≥ 70 years of age) patients, with favorable toxicity and a response rate of 50% among 10 evaluable patients. In preliminary results from a separate phase II trial, single-agent gefitinib has produced stable disease and symptom improvement in patients with a PS of 2 or 3. Based on this evidence, patients in this population may be reasonable candidates for EGFR-targeted therapies, but larger trials are needed before widespread use for this indication.
**APPROPRIATE DOSING AND LENGTH OF TREATMENT**

For NSCLC, gefitinib is administered at 700 mg/d, well below the maximum tolerated dose of 700 mg/d. In the IDEAL trials, use of gefitinib at 500 mg/d resulted in higher toxicities with no additional efficacy benefits compared with the 250 mg/d dose. Erlotinib is dosed at 150 mg/d. Trials are currently under way to investigate the use of higher and lower doses of erlotinib in advanced NSCLC.

For all patient subgroups, treatment with EGFR-TKIs should be maintained for as long as the patient continues to receive clinical benefit, including complete or partial response, stable disease, or symptom improvement. Progressive disease or symptom worsening indicate that treatment should be stopped and alternate options pursued.

**FUTURE DIRECTIONS**

In addition to gefitinib and erlotinib, other EGFR-TKIs are also under investigation in phase I/II trials. Many of these EGFR-TKIs have differing selectivities for the various members of the human EGFR family. CI-1033, a pan-erbB TKI, is a clinically promising agent that is active against all four members of the erbB receptor TK family. CI-1033 inhibition is highly selective for erbB1 (EGFR), erbB2, erbB3, and erbB4, and it is currently undergoing phase I clinical trials. As mentioned earlier, the monoclonal antibody cetuximab has been approved for the treatment of colorectal cancer, but phase III trials in lung cancer are pending. In addition, two humanized anti-EGFR antibodies, panitumumab and EMD 72000, are in early stages of development. The antiangiogenic vascular endothelial growth factor monoclonal antibody bevazicumab has also recently been approved to treat metastatic colorectal cancer. Chimeric molecules made by fusing portions of the genes for ligands (EGF, TGF-α) with a toxin gene provide another novel approach for targeting toxins to EGFR-expressing tumor cells. DAB389-EGF is one such fusion toxin currently in phase II clinical trials in NSCLC. Many of these targeted agents are being investigated in combination with each other and with standard chemotherapies. Much remains to be learned about the best use of these agents. The favorable tolerability profile of targeted agents has allowed their use in combinations and in patient types who would not otherwise have benefited. Promising results at this stage of investigation suggest that the future may yield even greater benefits for patients once the best use of targeted therapies is determined.

**CONCLUSIONS**

Increased knowledge of the mechanistic properties of malignant growth has facilitated the development of molecular-based therapies that can act on specific targets. Anti-EGFR antibodies and EGFR-TKIs have shown efficacy in treating patients with advanced NSCLC who have failed previous first-line and/or second-line cancer therapies. Meaningful benefits for patients with advanced NSCLC include tumor responses, stable disease, and improvements in symptoms and quality of life in about half of the treated patients. Inhibition of EGFR signaling has been shown to achieve these goals in patients when all prior cancer treatments have failed. Cytotoxic chemotherapy is often limited by severe systemic toxicities. With molecular-targeted therapies, maximum antitumor effects may be achieved at doses that are considerably below the maximum tolerated dose. Adverse events are mild, manageable, and reversible on treatment cessation. Collectively, these findings support the use of targeted agents for improving the clinical outcomes and quality of life in patients with advanced NSCLC. These agents should be considered as a treatment option for patients who have failed or are ineligible for traditional chemotherapy. The American Society of Clinical Oncology and the National Comprehensive Cancer Network have recently reviewed and revised their consensus-based practice guidelines for NSCLC; in these guidelines, targeted therapies are recommended as second-line therapy if platinum/docetaxel combination is used as first-line therapy, and as third-line therapy if docetaxel is used as second-line therapy.

The management of patients with NSCLC is best done in a multidisciplinary fashion. Pulmonologists have a key role in the diagnosis, staging, pretreatment assessment, and in the follow-up of patients after treatment for lung cancer. But more importantly, as pulmonologists are often the first to clinically evaluate patients with lung cancer, we play an especially important role in the referral of lung cancer patients, regardless of their stage of disease, to the appropriate subspecialist for treatment. Previously, it has been shown that not all patients are referred to medical oncologists because of a belief by pulmonologists and surgeons that the survival benefit is outweighed by the toxicities associated with chemotherapy. These new agents offer a promising treatment option for patients with advanced lung cancer, and as such these patients should be referred to a medical oncologist for consideration of treatment. While they should not be mistaken for the “magic bullet” that will cure lung cancer, this strategy represents a fundamental shift in how lung cancer is likely to be treated in the future.
References

12 Raymond E, Fairev S, Armand JP. Epidermal growth factor receptor tyrosine kinase as a target for anticancer therapy. Drugs 2000; 60(suppl 1):15–23
24 Mendelsohn J. The epidermal growth factor receptor as a target for cancer therapy. Endocr Relat Cancer 2001; 8:3–9
27 Ochs J, Gros J, Warner KL. Final survival and safety results for 21,064 non-small cell lung cancer (NSCLC) patients who received compassionate use gefitinib (Iressa®) in a United States expanded access program (EAP) [abstract]. Proc Am Soc Clin Oncol 2004; 23:628
34 Mendelsohn J. The epidermal growth factor receptor as a target for cancer therapy. Endocr Relat Cancer 2001; 8:3–9
44 Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung
50 Slichenmyer WJ, Elliott WL, Fry DW. CI-1033, a pan-erbB tyrosine kinase inhibitor. Semin Oncol 2001; 28(suppl16): 80–85