REVIEW ARTICLE

DRUG THERAPY

EGFR Antagonists in Cancer Treatment

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Cancer cells may acquire the capacity for autonomous and dysregulated proliferation through the uncontrolled production of specific molecules that promote cell growth (growth factors) or through abnormal, enhanced expression of specific proteins (growth factor receptors) on the cell membranes to which growth factors selectively bind. Both processes trigger a series of intracellular signals that ultimately lead to the proliferation of cancer cells, induction of angiogenesis, and metastasis.[1] The majority of human epithelial cancers are marked by functional activation of growth factors and receptors of the epidermal growth factor receptor (EGFR) family. Given this phenomenon, EGFR was the first growth factor receptor to be proposed as a target for cancer therapy. After 20 years of drug development, four EGFR antagonists are currently available for the treatment of four metastatic epithelial cancers: non–small-cell lung cancer, squamous-cell carcinoma of the head and neck, colorectal cancer, and pancreatic cancer. Less information is available about the use of EGFR antagonists in the treatment of earlier stages of cancer. This article summarizes the mechanisms of action of EGFR inhibitors, presents the clinical evidence of their anticancer activity, and considers the current, and controversial, clinical issues with respect to their optimal use in the treatment of patients with cancer.

EGFR IN HUMAN CARCINOGENESIS

EGFR is a transmembrane receptor belonging to a family of four related proteins (Fig. 1).[2] Ten different ligands can selectively bind to each receptor. After a ligand binds to a single-chain EGFR, the receptor forms a dimer[3] that signals within the cell by activating receptor autophosphorylation through tyrosine kinase activity.[3] Autophosphorylation triggers a series of intracellular pathways that may result in cancer-cell proliferation, blocking apoptosis, activating invasion and metastasis, and stimulating tumor-induced neovascularization.[3,4]

DEVELOPMENT OF EGFR ANTAGONISTS FOR ANTICANCER THERAPY

The first anti-EGFR drugs were developed in the 1980s.[18] Two classes of EGFR antagonists have been successfully tested in phase 3 trials and are now in clinical use: anti-EGFR monoclonal antibodies and small-molecule EGFR tyrosine kinase inhibitors (Tables 1 and 2).[4,5,10-12,18]

Anti-EGFR monoclonal antibodies, such as cetuximab, bind to the extracellular domain of EGFR when it is in the inactive configuration, compete for receptor binding by occluding the ligand-binding region, and thereby block ligand-induced EGFR tyrosine kinase activation.[4,5,19] Small-molecule EGFR tyrosine kinase inhibitors, such as erlotinib and gefitinib, compete reversibly with ATP to bind to the intracellular catalytic domain of EGFR tyrosine kinase and, thus, inhibit EGFR autophosphorylation and downstream signaling. Anti-EGFR monoclonal antibodies recognize EGFR

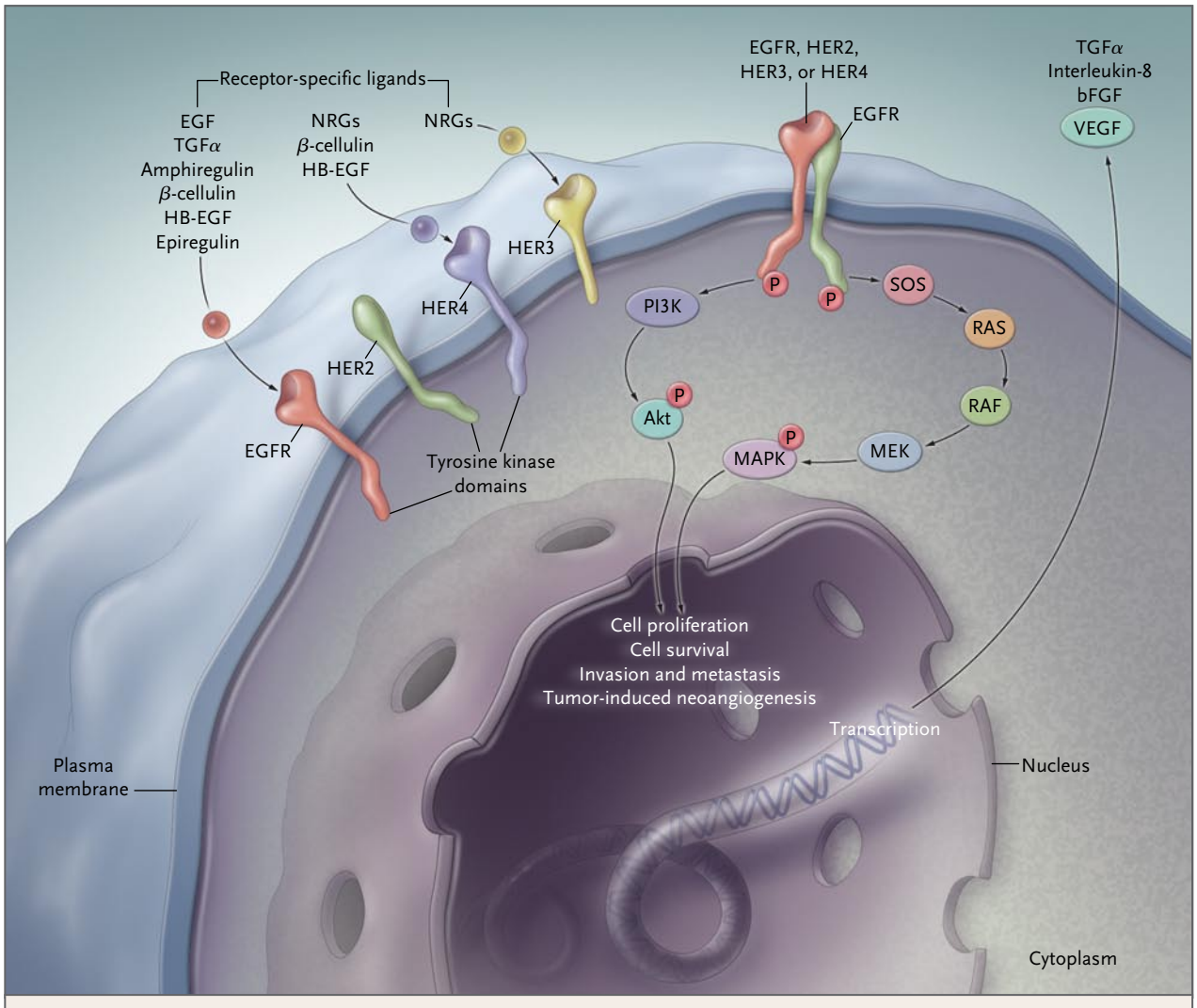

Figure 1. Signal Transduction Pathways Controlled by the Activation of EGFR.

Three steps can be schematically defined in the activation of EGFR-dependent intracellular signaling.[2-17] First, the binding of a receptor-specific ligand occurs in the extracellular portion of the EGFR or of one of the EGFR-related receptors (HER2, HER3, or HER4). Second, the formation of a functionally active EGFR-EGFR dimer (homodimer) or of an EGFR-HER2, EGFR-HER3, or EGFR-HER4 dimer (heterodimer) causes the ATP-dependent phosphorylation of specific tyrosine residues in the EGFR intracellular domain. Third, this phosphorylation triggers a complex program of intracellular signals to the cytoplasm and then to the nucleus. The two major intracellular pathways activated by EGFR are the RAS–RAF–MEK–MAPK pathway, which controls gene transcription, cell-cycle progression from the G1 phase to the S phase, and cell proliferation, and the PI3K–Akt pathway, which activates a cascade of anti-apoptotic and prosurvival signals. bFGF denotes basic fibroblast growth factor, HB-EGF heparin-binding EGF, MAPK mitogen-activated protein kinase, P phosphate, PI3K phosphatidylinositol 3,4,5-kinase, TGFα transforming growth factor α, and VEGF vascular endothelial growth factor. For more detailed information, see Figure 1 in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

exclusively and are therefore highly selective for this receptor. In addition, various small-molecule EGFR tyrosine kinase inhibitors can block different growth factor receptor tyrosine kinases, including other members of the EGFR family, or the vascular endothelial growth factor receptor. Various irreversible EGFR tyrosine kinase inhibitors are now in early stages of clinical development.[4,5,12] The mechanism (or mechanisms) of action, pharmacologic effects, and spectrum of activity of anti-EGFR monoclonal antibodies and small-molecule EGFR tyrosine kinase inhibitors have differences that may be relevant for clinical activity (Table 1 and Fig. 2 and 3).[13]

Table 1. Functional and Pharmacologic Characteristics of EGFR Inhibitors.*

Characteristic	Blocking Monoclonal Antibodies	Small-Molecule Tyrosine Kinase Inhibitors
Route of administration	Intravenous (generally once a week or every 2 wk)	Oral (generally daily continuous dosing)
Structure	Recombinant immunoglobulins (150–180 kD)	Low-molecular-weight compounds (400–600 kD)
Target selectivity	Exclusively specific for EGFR	Relatively specific for EGFR; may inhibit only one or all EGFR family receptors; some EGFR tyrosine kinase inhibitors also inhibit other growth factor receptors (e.g., dual inhibitors of EGFR and VEGFR)
Mechanism of interference with EGFR activation	Bind extracellular portion of receptor, preventing ligand binding and receptor dimerization by occluding ligand region (cetuximab)	Bind intracellular portion of receptor within tyrosine kinase domain, generally by competing with ATP and inhibiting receptor autophosphorylation; most are reversible; irreversible EGFR tyrosine kinase inhibitors are in clinical development
Cellular effects of EGFR inhibition	Inhibit cancer-cell proliferation (G1 phase arrest), angiogenic growth factor production (VEGF) and tumor-induced angiogenesis, and cancer-cell invasion; potentiate antitumor activity of cytotoxic drugs and radiotherapy	Inhibit cancer-cell proliferation (G0–G1 phase arrest), angiogenic growth factor production (VEGF) and tumor-induced angiogenesis, and cancer-cell invasion; potentiate antitumor activity of cytotoxic drugs and radiotherapy
Induction of EGFR internalization, down-regulation, and degradation	Yes	No (although irreversible EGFR tyrosine kinase inhibitors can cause EGFR degradation and subsequent EGFR down-regulation)
Inhibition of EGFR-dependent intracellular signaling	Yes	Yes
Activity against mutant EGFR proteins	Probably yes, for mutations of EGFR tyrosine kinase domain, since anti-EGFR monoclonal antibodies bind to EGFR extracellular domain; not completely known for mutations of EGFR extracellular domain	Yes, for most mutations of EGFR tyrosine kinase domain (mutation in codons 746–750 in exon 19 and L858R in exon 21), since these EGFR mutant proteins bind with higher-affinity small-molecule EGFR tyrosine kinase inhibitors, such as erlotinib or gefitinib; no, for gefitinib- or erlotinib-acquired EGFR-resistance mutation (T790M in exon 20), although several new-generation EGFR tyrosine kinase inhibitors that are active against mutant EGFR proteins are in early clinical development
Activation of host immune response	Yes — antibody-dependent cytotoxicity may significantly contribute to anticancer activity of some anti-EGFR monoclonal antibodies, such as cetuximab; however, no antibody-dependent cytotoxicity has been reported for panitumumab	No

* EGFR denotes epidermal growth factor receptor, VEGF vascular endothelial growth factor, and VEGFR VEGF receptor.

CLINICAL EFFICACY OF EGFR ANTAGONISTS IN HUMAN CANCERS

More than 10 EGFR-targeting agents are in advanced clinical development for the treatment of various human cancer types.[5,10,11,12] Two anti-EGFR monoclonal antibodies (cetuximab and panitumumab) and two small-molecule, reversible EGFR tyrosine kinase inhibitors (gefitinib and erlotinib) have been approved in several countries for the treatment of metastatic non–small-cell lung cancer, colorectal cancer, squamous-cell carcinoma of the head and neck, and pancreatic cancer (Table 2).[20-24] (For relevant clinical studies supporting the use of anti-EGFR drugs in the first three conditions, see Tables 1, 2, and 3 in the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

NON–SMALL-CELL LUNG CANCER

Phase 1 trials showed that gefitinib and erlotinib have important clinical activity in patients with

Table 2. EGFR Inhibitors Currently Approved for Cancer Treatment.*

Drug	Molecular Properties	Approved Uses
Erlotinib	Reversible EGFR tyrosine kinase inhibitor (quinazoline-derivative molecule)	Erlotinib has been approved by several regulatory agencies worldwide, including the FDA and the EMEA in the European Union, as monotherapy for the treatment of non–small-cell lung cancer that is refractory to platinum-based chemotherapy. More recently, erlotinib has been approved by the FDA and the EMEA for use in combination with gemcitabine as first-line treatment for advanced pancreatic cancer.
Gefitinib	Reversible EGFR tyrosine kinase inhibitor (quinazoline-derivative molecule)	Gefitinib has been approved in various countries for use as third-line treatment of non–small-cell lung cancer that is refractory to platinum-based and docetaxel-based chemotherapy regimens. After an accelerated approval process, it was approved by the FDA in May 2003 but has been withheld from the U.S. market since June 2005, as a result of the release of preliminary results of the ISEL trial, which assessed its use in patients with non–small-cell lung cancer that was refractory to previous platinum-based chemotherapy. Gefitinib has never been approved in the European Union but is currently on the market in Japan, Korea, China, and several other Asian countries. It is currently an investigational drug in the United States and the European Union.
Cetuximab	Human–mouse chimeric monoclonal antibody (IgG1 subtype)	Cetuximab has been approved by several regulatory agencies worldwide, including the FDA and the EMEA, for the treatment of advanced colorectal cancer that is refractory to irinotecan-based chemotherapy (alone or in combination with irinotecan in the United States but only in combination with irinotecan in the European Union). Cetuximab in combination with radiotherapy is also approved for the treatment of locally advanced squamous-cell carcinoma of the head and neck.
Panitumumab	Fully human monoclonal antibody (IgG2κ subtype)	Panitumumab has been approved by several regulatory agencies worldwide, including the FDA, as monotherapy for third-line treatment of colorectal cancer that is refractory to fluoropyrimidines, oxaliplatin, or irinotecan. In December 2007, panitumumab was approved by the EMEA for use in patients with colorectal cancer who carry a normal, wild-type *K-RAS* gene.

* EGFR denotes epidermal growth factor receptor, EMEA European Medicines Evaluation Agency, FDA Food and Drug Administration, and ISEL Iressa Survival Evaluation in Lung Cancer.

metastatic, chemorefractory non–small-cell lung cancer.[25-29] Dose-dependent and reversible diarrhea and acneiform rashes have been the most prominent side effects (maximum tolerated dose, 750 mg per day for gefitinib and 150 mg per day for erlotinib). The histologic characteristics of the rash (a neutrophilic infiltrate in perifollicular areas within the basal layer of the skin) differ from those seen in typical acne and are common to all EGFR-targeted drugs, including anti-EGFR monoclonal antibodies.[30] Skin toxicity is generally observed within 2 to 3 weeks after the start of treatment and gradually resolves in most patients, even when anti-EGFR treatment is continued. The maximum tolerated dose of erlotinib (150 mg per day), based on side effects, was chosen for further study, whereas for gefitinib, relatively low doses (patients were randomly assigned to receive 250 mg or 500 mg per day), given the maximum tolerated doses, were chosen.

Gefitinib was the first anti-EGFR agent that was shown, in two randomized phase 2 studies, to have clinically important antitumor activity in patients with non–small-cell lung cancer who had not had a response to one or more chemotherapy regimens, including platinum-based and docetaxel-based therapies.[30-32] The two doses of gefitinib (250 mg and 500 mg) had similar antitumor activity, but toxicity was greater at the higher dose. Therefore, the lower dose was selected for further clinical studies. These trials led the Food and Drug Administration (FDA) in May 2003 to approve gefitinib as third-line therapy for patients with locally advanced or metastatic non–small-cell lung cancer after failure of both platinum-based and docetaxel-based chemotherapies.

However, a placebo-controlled, randomized phase 3 trial (the Iressa Survival Evaluation in Lung Cancer [ISEL] trial) failed to show that gefitinib was effective in improving survival.[33] Neither median survival nor the rate of survival at 1 year differed significantly between patients receiving gefitinib and those receiving placebo in either the overall study population or a subgroup with a history of adenocarcinoma. Pre-

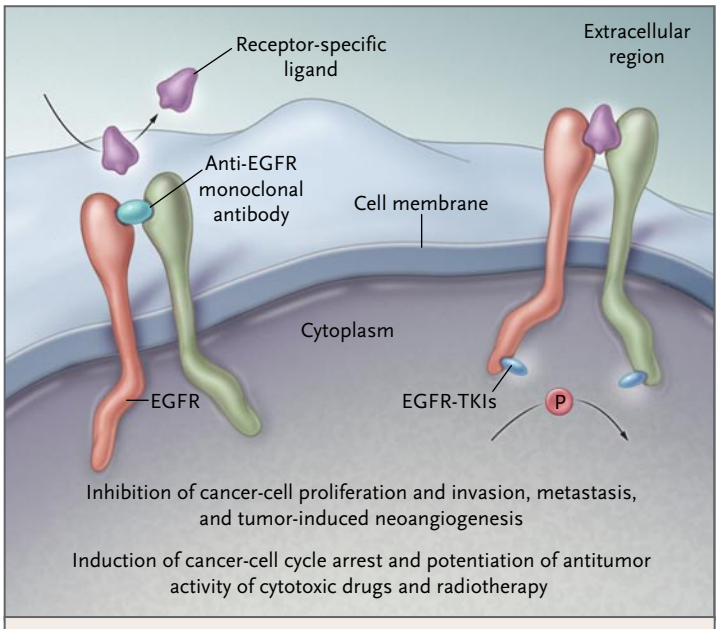

Figure 2. Mechanisms of Action of Anti-EGFR Drugs in Cancer Cells.

Anti-EGFR monoclonal antibodies bind to the extracellular domain of EGFR and block ligand binding and receptor activation. Small-molecule EGFR tyrosine kinase inhibitors (TKIs) compete with ATP to bind to the intracellular EGFR tyrosine kinase catalytic domain and thus block EGFR autophosphorylation and downstream signaling. As a consequence of treatment with these drugs, key EGFR-dependent intracellular signals in cancer cells are affected. There is inhibition of cancer-cell proliferation (blockade of cell-cycle progression and G1 arrest through an increase in the $p27^{kip1}$ inhibitor of cyclin-dependent kinases); inhibition of tumor-induced angiogenesis by blockade of cancer-cell production of angiogenic factors, including transforming growth factor α, vascular endothelial growth factor, interleukin-8, and basic fibroblast growth factor; inhibition of cancer-cell invasion and metastasis; and potentiation of antitumor activity of cytotoxic drugs and radiotherapy.[6-9,11,109-112]

planned subgroup analysis showed a significant survival benefit only in patients of Asian origin and in those who had never smoked. In June 2005, on the basis of the lack of a survival benefit in the ISEL study, the FDA restricted the use of gefitinib to patients participating in a clinical trial or continuing to benefit from treatment already initiated. Currently, gefitinib is marketed in several countries in eastern Asia but is not available in the United States or the European Union.

More recently, two randomized phase 3 trials evaluated the effectiveness of gefitinib monotherapy as compared with that of standard chemotherapy (docetaxel) as second-line treatment for chemotherapy-refractory non–small-cell lung cancer. The V-15-32 trial, conducted in Japan, failed to demonstrate the noninferiority of gefitinib in terms of overall survival, which was the primary end point.[34] However, in a large multicenter trial, this end point was achieved with gefitinib after platinum-based therapy had failed.[35] In addition, the side-effect profile appeared to favor gefitinib.[35]

In a phase 2 study, the antitumor activity of erlotinib as a single agent in heavily pretreated non–small-cell lung cancer was similar to that of gefitinib.[36] More important, in the BR.21 trial, a phase 3, randomized, double-blind, placebo-controlled study involving patients with pretreated non–small-cell lung cancer, erlotinib increased median survival by approximately 2 months as compared with placebo (Table 3).[37] Responses were significantly more frequent in women, in patients with adenocarcinoma, and in patients with no history of smoking. However, a significant survival advantage was observed in all patient subgroups after treatment with erlotinib as compared with placebo. Quality-of-life analysis supported the palliative benefit of erlotinib in extending the time during which patients were free of symptoms (cough, dyspnea, and pain).[38] On the basis of these results, erlotinib was approved by the FDA in November 2004 and by the European Medicines Evaluation Agency (EMEA) in October 2005 for second- and third-line treatment of chemotherapy-resistant, advanced non–small-cell lung cancer. Several hypotheses have been proposed as to why the efficacy seems different for gefitinib and erlotinib in the similar BR.21 and ISEL phase 3 studies. One possible explanation is dosing: erlotinib was used at the maximum tolerated dose, whereas gefitinib was provided at a much lower dose.[39]

On the basis of preclinical data demonstrating that anti-EGFR drugs potentiate the antitumor activity of cytotoxic drugs, four phase 3, double-blind, placebo-controlled, randomized clinical trials examined the combination of erlotinib or gefitinib with chemotherapy as first-line treatment for non–small-cell lung cancer. Two standard platinum-based, dual-drug regimens were used in combination with erlotinib or gefitinib.[40-43] Neither a survival advantage nor a benefit with respect to the response rate or time to progression was seen with the addition of gefitinib or erlotinib to chemotherapy in any of these trials. One possible reason that these trials failed to demonstrate any advantage of gefitinib or erlotinib is that they were conducted in

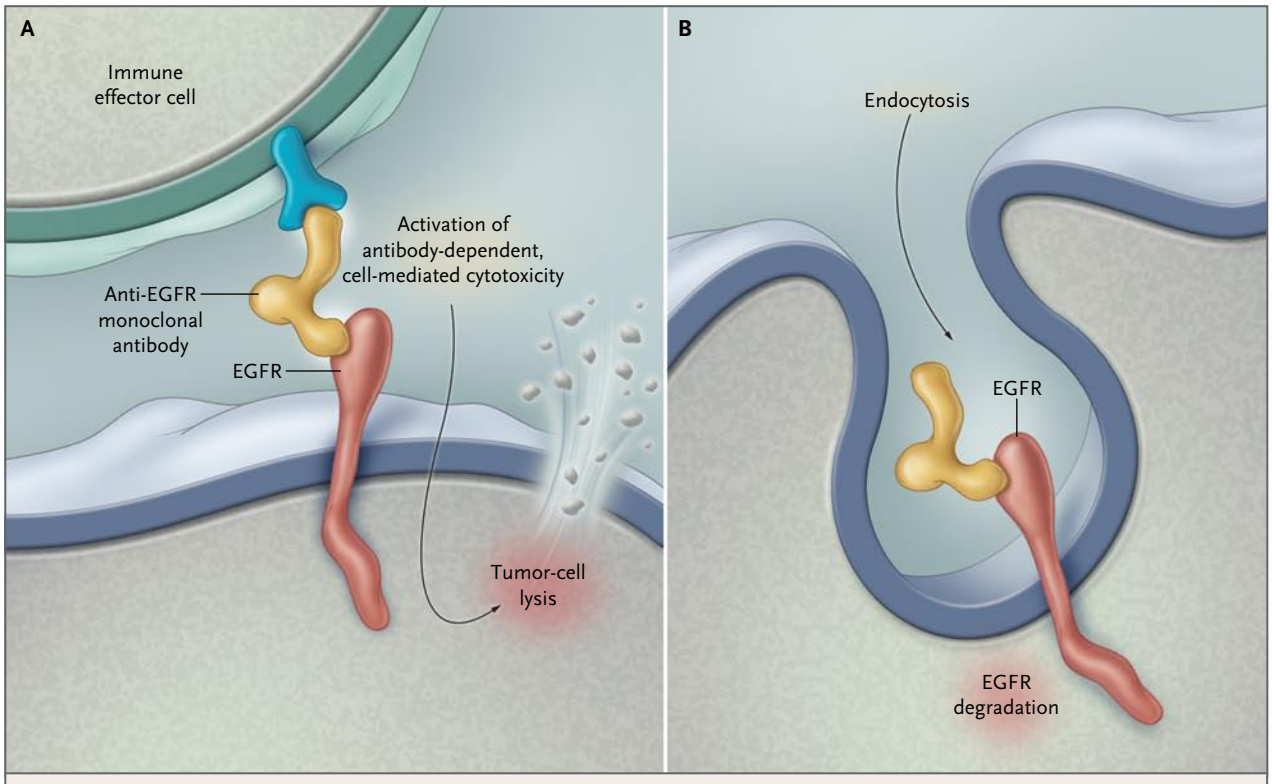

Figure 3. Mechanisms of Action of Anti-EGFR Monoclonal Antibodies in Cancer Cells.

The mechanisms of action and pharmacologic effects of anti-EGFR monoclonal antibodies and small-molecule EGFR tyrosine kinase inhibitors do not completely overlap, and some of the differences between them may be clinically relevant (see Table 1). In particular, the anti-EGFR monoclonal antibody cetuximab, which is an IgG1 immunoglobulin, could elicit host antitumor immune responses, including antibody-dependent, cell mediated cytotoxicity (Panel A). Furthermore, anti-EGFR monoclonal antibodies can induce EGFR cellular internalization and down-regulation, thereby enhancing receptor degradation (Panel B). These two mechanisms could make an important contribution to antitumor activity.

unselected patients with non–small-cell lung cancer.[44] Since only a subgroup of EGFR-positive patients with non–small-cell lung cancer have tumors that are dependent on the EGFR pathway, few patients with this type of cancer would have a clinical benefit from the addition of an anti-EGFR drug to chemotherapy.[44] In addition, a retrospective subgroup analysis suggested that the addition of erlotinib to carboplatin and paclitaxel significantly prolonged survival only in the subgroup of patients who had never smoked.[42]

Cetuximab treatment is said to have relatively few side effects. The most common adverse events include skin toxicity (flushing, an acnelike rash, and folliculitis), fever and chills, asthenia, transient elevations in aminotransferase levels, and nausea.[45] Approximately 1.5% of patients have infusion reactions, which include allergic reactions requiring discontinuation of therapy; this rate is in keeping with the use of a chimeric human–mouse monoclonal antibody. Whereas cetuximab is marginally active as a single agent in advanced non–small-cell lung cancer, most phase 2 studies suggest that adding cetuximab to platinum-based therapies is of clinical benefit.[46-50] A large, multicenter, randomized, phase 3 study in which cetuximab was added to standard platinum-based chemotherapy (cisplatin and vinorelbine) has recently been completed (ClinicalTrials.gov number, NCT00148798). A more thorough evaluation of the role of cetuximab in the treatment of advanced non–small-cell lung cancer awaits publication of the results of this trial.

COLORECTAL CANCER

Cetuximab has been evaluated in both chemotherapy-refractory and untreated metastatic colorec-

Table 3. Efficacy of Erlotinib in Chemotherapy-Refractory Non–Small-Cell Lung Cancer.*

Variable	Placebo (N=243)	Erlotinib (N=488)	Hazard Ratio (95% CI)	P Value
Overall response rate (%)†	<1	9		<0.001
Median progression-free survival (mo)	1.8	2.2	0.61 (0.51–0.74)	<0.001
Median overall survival (mo)	4.7	6.7	0.70 (0.58–0.85)	0.001

* Patients with metastatic, platinum-refractory, non–small-cell lung cancer were treated either with erlotinib alone (150 mg per day) or with placebo until disease progression. Approximately half of the patients had also received a second-line treatment before study entry. Data are from Shepherd et al.[37] CI denotes confidence interval.
† The overall response rate included complete and partial responses.

tal cancer. In phase 2 studies, cetuximab monotherapy was associated with response rates of 9 to 12%. Response rates of approximately 20% were achieved when cetuximab was used in combination with irinotecan in patients who had not had a response to previous therapy with irinotecan.[51-53] A multicenter, randomized, phase 2 trial evaluated the activity of cetuximab given alone or with irinotecan in patients who had not had a response to irinotecan monotherapy (Table 4).[54] The cetuximab–irinotecan combination was significantly more effective than cetuximab monotherapy in terms of the response rate and rate of progression-free survival. However, the median survival was similar with the two approaches, mainly because of the crossover of patients from cetuximab monotherapy to the combination group on treatment failure. On the basis of these results, cetuximab was approved by the FDA in February 2004 for use in patients with metastatic colorectal cancer, either in combination with irinotecan (for patients who do not have a response to irinotecan alone) or as monotherapy (in patients who cannot tolerate irinotecan). The EMEA has approved cetuximab only in combination with irinotecan.

A multicenter, randomized, phase 3 trial examined the combination of cetuximab plus irinotecan as second-line treatment for colorectal cancer in patients who had not had a response to an oxaliplatin-based regimen. Cetuximab plus irinotecan was significantly better than irinotecan alone in improving response rates, increasing progression-free survival, and improving the quality of life.[55] However, no differences were seen in overall survival, probably because almost half the patients crossed over to cetuximab treatment after the failure of irinotecan monotherapy. Recently, a randomized phase 3 trial comparing the use of cetuximab with best supportive care for patients in whom all available drugs, including fluoropyrimidines, oxaliplatin, and irinotecan, had failed showed that cetuximab increased progression-free survival, overall survival, and quality of life (Table 4).[56] Cetuximab appears to be the only drug that does so with colorectal cancer who have had unsuccessful courses of all currently available chemotherapies.

Phase 2 studies[57,58] indicate that cetuximab combined with both irinotecan and oxaliplatin-based chemotherapies may have a role in the first-line treatment of metastatic colorectal cancer, with a 10 to 20% absolute increase in response rates reported. Such a response could be clinically relevant, particularly for the management of metastatic disease limited to the liver, since reductions in the number and size of metastases after administration of the drug might present the opportunity for potentially curative surgery. Recently, a multicenter, randomized, phase 3 study evaluated the combination of cetuximab with a standard chemotherapeutic regimen of fluorouracil, leucovorin, and irinotecan (FOLFIRI) in previously untreated metastatic colorectal cancer. Cetuximab plus FOLFIRI significantly increased response rates, prolonged progression-free survival, and increased the number of patients who could undergo potentially curative surgical removal of liver metastasis by a factor of approximately three.[59]

Another monoclonal agent is panitumumab, a fully human anti-EGFR monoclonal antibody.[22] As seen with cetuximab, skin toxicity and diarrhea are the most common side effects of this agent. A randomized phase 3 clinical trial compared the use of panitumumab with the best supportive care in patients with colorectal cancer who had previously been treated unsuccessfully with a fluoropyrimidine, oxaliplatin, and irinotecan. A 10% response rate was reported,

together with a significant reduction in the risk of tumor progression.[60] However, no difference was observed in overall survival, probably because of the preplanned crossover to panitumumab in the treatment group receiving the best supportive care. On the basis of these results, panitumumab was approved by the FDA in September 2006 as monotherapy for the treatment of metastatic colorectal cancer with disease progression after chemotherapy regimens consisting of a fluoropyrimidine, oxaliplatin, and irinotecan.

SQUAMOUS-CELL CARCINOMA OF THE HEAD AND NECK

The combination of cetuximab and radiotherapy was initially tested in patients with previously untreated, locally advanced squamous-cell carcinoma of the head and neck. In a randomized, multicenter, phase 3 clinical trial, patients were treated with radiotherapy alone or in combination with cetuximab (Table 5).[61,62] Radiotherapy plus cetuximab significantly prolonged progression-free survival, duration of locoregional control, and overall survival. A randomized phase 3 trial of cisplatin plus cetuximab as compared with placebo in patients with previously untreated, metastatic squamous-cell carcinoma of the head and neck showed a significantly higher response rate in the group that received cisplatin plus cetuximab.[63] However, no significant difference in overall survival was observed, possibly because of the relatively small study sample. A recent larger, randomized, multicenter phase 3 trial showed that the addition of cetuximab to platinum- and fluorouracil-based chemotherapy in the first-line treatment of recurrent or metastatic squamous-cell carcinoma of the head and neck may be helpful, since progression-free survival and overall survival were significantly prolonged (Table 5).[62] This phase 3 study is unique in showing a survival benefit for a novel treatment as compared with platinum-based chemotherapy in the treatment of this disease.

Several phase 2 studies evaluated cetuximab alone or in combination with cisplatin in the treatment of platinum-resistant squamous-cell carcinoma of the head and neck, a cancer in which no specific therapy has been effective; such patients have a very short life expectancy. The overall response rate with cetuximab monotherapy was 10 to 13%, with a disease-control rate of ap-

Table 4. Efficacy of Cetuximab in Chemotherapy-Refractory Colorectal Cancer.*

Variable	Cetuximab (N = 111)†	Cetuximab plus Irinotecan (N = 218)	Hazard Ratio (95% CI)	P Value	Best Supportive Care (N = 285)	Cetuximab (N = 287)	Hazard Ratio (95% CI)	P Value
BOND trial‡:								
Overall response rate (%)§	10.8	22.9		0.007				
Median time to progression (mo)	1.5	4.1	0.54 (0.42–0.71)	<0.001				
Median overall survival (mo)	6.9	8.6	0.91 (0.68–1.21)	NS				
NCIC-CO.17 trial¶								
Overall response rate (%)§					0	8		<0.001
Median progression-free survival (mo)					1.8	1.9	0.68 (0.57–0.80)	<0.001
Median overall survival (mo)					4.6	6.17	0.77 (0.64–0.92)	0.005

* CI denotes confidence interval, and NS not significant.
† Crossover to cetuximab plus irinotecan was allowed after progression in 56 patients (50%) treated initially with cetuximab alone.
‡ The Bowel Oncology with Cetuximab Antibody (BOND) trial was a randomized phase 2 trial. Patients with metastatic, irinotecan-refractory colorectal cancer were treated either with cetuximab alone (intravenous loading dose of 400 mg per square meter of body-surface area, followed by weekly intravenous doses of 250 mg per square meter) or with cetuximab (loading dose of 400 mg per square meter followed by 250 mg per square meter weekly) plus irinotecan until disease progression. Approximately two thirds of the patients had also received a line of treatment for metastatic disease with an oxaliplatin-based therapy before study entry. Data are from Cunningham et al.[54]
§ The overall response rate included complete and partial responses.
¶ The NCIC-CO.17 trial was a randomized phase 3 trial. Patients with metastatic colorectal cancer that was refractory to fluorouracil, irinotecan, and oxaliplatin were treated either with cetuximab alone (intravenous loading dose of 400 mg per square meter, followed by weekly intravenous doses of 250 mg per square meter) or with best supportive care until disease progression. Crossover to cetuximab was not allowed after progression in the group that received best supportive care. Data are from Jonker et al.[55]

Table 5. Efficacy of Cetuximab in Squamous-Cell Carcinoma of the Head and Neck.*

Study	Radiotherapy (N=213)	Radiotherapy plus Cetuximab (N=211)	Hazard Ratio (95% CI)	P Value	Chemotherapy (N=220)	Chemotherapy plus Cetuximab (N=222)	Hazard Ratio (95% CI)	P Value
Bonner et al.†								
Overall response rate (%)‡	64	74	0.57 (0.36–0.90)	0.02				
Median locoregional control	14.9	24.4	0.68 (0.52–0.89)	<0.005				
Median progression-free survival (mo)	12.4	17.1	0.70 (0.54–0.90)	<0.006				
Median overall survival (mo)	29.3	49.0	0.74 (57–0.97)	<0.03				
EXTREME trial§								
Overall response rate (%)‡					19.5	35.6		0.001
Median progression-free survival (mo)					3.3	5.6	0.54 (0.43–0.67)	<0.001
Median overall survival (mo)					7.4	10.1	0.80 (0.64–0.98)	0.04

* CI denotes confidence interval.
† This study[61] was a randomized phase 3 trial of radiotherapy alone or radiotherapy plus cetuximab in locally advanced disease. Patients with locally advanced squamous-cell carcinoma of the head and neck were treated either with radiotherapy alone or with radiotherapy plus cetuximab (intravenous loading dose of 400 mg per square meter of body-surface area, followed by weekly intravenous doses of 250 mg per square meter for the duration of radiotherapy).
‡ The overall response rate includes complete and partial responses.
§ The Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME) trial was a randomized phase 3 trial of chemotherapy alone or chemotherapy plus cetuximab as first-line treatment in metastatic disease. Patients with metastatic squamous-cell carcinoma of the head and neck were treated with platinum–fluorouracil chemotherapy or with the same chemotherapy plus cetuximab (intravenous loading dose of 400 mg per square meter, followed by weekly intravenous doses of 250 mg per square meter) until disease progression. Crossover to cetuximab was not allowed after progression in the group that received chemotherapy alone. Data are from Vermorken et al.[62]

proximately 40 to 46%.[64-67] Cetuximab was approved by the FDA in February 2006 for use in combination with radiotherapy to treat patients with locally advanced, unresectable squamous-cell carcinoma of the head and neck. It was also approved as monotherapy for metastatic disease in patients who have not had a response to chemotherapy. In March 2006, the EMEA approved cetuximab in combination with radiotherapy for the treatment of locally advanced disease.

PANCREATIC CANCER

A single-group phase 2 study suggested that cetuximab was promising when used in combination with gemcitabine for the treatment of advanced pancreatic cancer.[68] However, a more recent randomized phase 3 study failed to show a significant survival advantage with this combination as compared with standard treatment (gemcitabine monotherapy).[69] In contrast, another randomized phase 3 trial, which compared the combination of erlotinib (100 mg per day) and gemcitabine with gemcitabine alone, showed a significant improvement in response and survival rates (hazard ratio for death, 0.82; 95% confidence interval, 0.69 to 0.99; P=0.04; 1-year survival rate, 23% vs. 17%, P=0.02), and both the FDA and EMEA have approved this regimen for first-line treatment of pancreatic cancer.[70] Although the increase in survival could be considered modest in absolute terms, it showed that there is a significant advantage in adding an anticancer drug to gemcitabine in the treatment of metastatic pancreatic cancer — a unique finding.

PREDICTING THE RESPONSE TO ANTI-EGFR DRUGS

Since only a subgroup of patients with cancer have a clinical benefit from treatment with EGFR inhibitors, there is an urgent need for identification and clinical validation of useful criteria for selecting patients for such treatment. A series of studies suggests that considering certain clinicopathological characteristics, as well as specific gene alterations, might help to identify patients whose cancers could be either sensitive or resistant to anti-EGFR therapy.

CLINICAL AND PATHOLOGICAL PREDICTORS

Most clinical studies of gefitinib or erlotinib in non–small-cell lung cancer suggest that Asian

ethnic background, female sex, the absence of a history of smoking, and a tumor with histologic features of adenocarcinoma are potential predictors of a positive clinical response to anti-EGFR therapy.[20,23,71] However, the presence or absence of cutaneous toxic effects, such as an acnelike rash, and their severity are the most important clinical correlates of the efficacy of anti-EGFR therapy. In fact, a significant positive correlation between cutaneous toxicity and rates of response, progression-free survival, and overall survival has been noted in virtually all trials of erlotinib, cetuximab, or panitumumab in advanced non–small-cell lung cancer, colorectal cancer, squamous-cell carcinoma of the head and neck, and pancreatic cancer.[53,54,72] It is conceivable that the effects in skin not influenced by cancer reflect the extent of EGFR blockade achieved in the tumor, in which case the rash would correlate with EGFR saturation or with a relevant drug concentration within the tumor.

EGFR PROTEIN EXPRESSION

EGFR expression as determined by immunohistochemical methods was the first biomarker investigated as a potential predictor of response. However, most studies have failed to show any relationship between EGFR expression and the clinical activity of anti-EGFR drugs.[24,51] Cetuximab has also been shown to have clinical activity in patients with colorectal cancer that is negative for EGFR.[73] Similarly, in a prospective phase 2 clinical trial, the response to treatment with panitumumab in patients with metastatic colorectal cancer was similar whether EGFR protein expression was high, low, or negative, as assessed by immunohistochemical methods.[74] Collectively, these data suggest that immunohistochemical testing for EGFR is not an optimal method for identifying patients who may have a response to treatment with anti-EGFR drugs.

SOMATIC *EGFR* GENE MUTATIONS

The discovery that certain somatic mutations within the tyrosine kinase, ATP-binding domain of the *EGFR* gene are associated with a response to EGFR tyrosine kinase inhibitors in non–small-cell lung cancer suggested that the selection of patients through molecular screening might be feasible.[75,76] Approximately 90% of *EGFR* mutations affect small regions of the gene within exons (18 to 24) that code for the EGFR tyrosine kinase domain. The most common mutations are an in-frame deletion in exon 19 around codons 746 to 750 (accounting for 45 to 50% of *EGFR* mutations) and a missense mutation leading to a substitution of arginine for leucine at codon 858 (L858R) in exon 21 (35 to 45% of *EGFR* mutations).[6] Somatic *EGFR* mutations are found in approximately 5 to 15% of unselected white patients and in 25 to 35% of unselected Asian patients with non–small-cell lung cancer. These mutations seem to be limited to non–small-cell lung cancer, since they have rarely been detected in other types of human cancer. Somatic mutations in the *EGFR* gene are most frequently detected in a subpopulation of patients with this form of cancer who have one or more of the following characteristics: histologic features of adenocarcinoma and, in particular, nonmucinous bronchioloalveolar carcinoma; an absence of a history of smoking; an absence of *K-RAS* gene mutations; Asian ethnicity; and female sex.[77-80] The likelihood of *EGFR* mutations decreases as the exposure to tobacco smoke increases, leading to the hypothesis that lung adenocarcinoma in patients who have never smoked is a distinct form of non–small-cell lung cancer with a high frequency of *EGFR* mutations and increased sensitivity to EGFR tyrosine kinase inhibitors.[81,82] The association between *EGFR* mutations and a response to erlotinib or gefitinib has been retrospectively confirmed in several clinical studies.[6] It has been also suggested that this association translates into improved survival.[6] However, in larger randomized studies, such as the BR.21 trial, a similar survival advantage was observed for patients treated with erlotinib, independently of the presence of *EGFR* mutations or of a wild-type *EGFR* gene, indicating that the presence of *EGFR* mutations is not the only biomarker for predicting a survival benefit of treatment with small-molecule EGFR tyrosine kinase inhibitors in patients with non–small-cell lung cancer.[83]

INCREASED *EGFR* COPY NUMBER

The *EGFR* gene is rarely amplified in human cancers. However, fluorescence in situ hybridization (FISH) shows an increased *EGFR* copy number with balanced polysomy in a high proportion of cancer cells in approximately 25 to 40% of patients with non–small-cell lung cancer, squamous-cell carcinoma of the head and neck, or colorectal cancer. A single-group, phase 2 trial of

treatment with gefitinib in advanced, chemotherapy-refractory non–small-cell lung cancer was the first to show that patients with FISH-positive tumors had significantly higher rates of response and survival than patients with FISH-negative tumors.[84] In the BR.21 trial, patients with FISH-positive tumors (approximately 40% of the patients) who were randomly assigned to receive erlotinib had significantly longer survival as compared with patients with FISH-positive tumors who received placebo. In the patients with FISH-negative tumors, there was no significant difference in survival.[83] Similar results were observed in the ISEL trial, which confirmed that patients with FISH-positive tumors who were treated with gefitinib had higher response rates and longer survival than patients receiving placebo.[85] No difference in survival was seen in FISH-negative patients, irrespective of treatment. However, FISH analysis failed to demonstrate any difference in progression-free survival or overall survival in a phase 3 trial that compared gefitinib with docetaxel as second-line therapy for advanced non–small-cell lung cancer (the Iressa Non–Small-Cell Cancer Trial Evaluating Response and Survival against Taxotene [INTEREST]).[36]

The predictive role of increased *EGFR* copy numbers has also been evaluated in patients with metastatic colorectal cancer in a series of retrospective studies. The first report on the correlation between positive results for EGFR and a response to therapy with cetuximab or panitumumab involved a small cohort of patients (31 patients) with advanced, chemotherapy-refractory colorectal cancer.[86] Recently, a FISH analysis of EGFR in tumor samples from patients enrolled in the phase 3 study comparing the use of panitumumab with best supportive care was reported.[87] In the group treated with panitumumab, patients with normal *EGFR* copy numbers had a shorter median progression-free survival and overall survival than patients with high *EGFR* copy numbers. Moreover, in the group treated only with best supportive care, no correlation between *EGFR* copy numbers and survival was observed, suggesting a predictive rather than a prognostic role of this genetic feature in patients with metastatic colorectal cancer who are treated with anti-EGFR monoclonal antibodies.

RESISTANCE TO EGFR ANTAGONISTS

INTRINSIC RESISTANCE

Activating mutations in the *K-RAS* gene, which result in EGFR-independent activation of the mitogen-activated protein kinase pathway, are found in approximately 15 to 30% of patients with non–small-cell lung cancer and 40 to 45% of patients with colorectal cancer, and their presence generally correlates with a worse prognosis with respect to the outcome of the cancer. *K-RAS* mutations occur in patients with a history of substantial cigarette use.[88,89] These mutations are most frequently recorded in codons 12 and 13 in the exon 2 of the *K-RAS* gene and are generally mutually exclusive with *EGFR* mutations. In several studies, *K-RAS* mutations have been significantly associated with lack of response to EFGR tyrosine kinase inhibitors in patients with non–small-cell lung cancer and with lack of response to cetuximab or to panitumumab in patients with advanced, chemotherapy-refractory colorectal cancer. Both findings suggest that EGFR-independent, constitutive activation of the K-RAS signaling pathway could impair the response to anti-EGFR drugs.[90-98] However, no correlation between *K-RAS* mutations and efficacy was reported in the INTEREST trial, which compared docetaxel and gefitinib as second-line treatments for non–small-cell lung cancer.[35] In contrast, the results of the phase 3 trial comparing the use of panitumumab with best supportive care in chemotherapy-refractory colorectal cancer have confirmed that the efficacy of panitumumab is limited to patients whose tumors carry the wild-type *K-RAS* gene.[99]

ACQUIRED RESISTANCE

In patients with non–small-cell lung cancer that initially responds to gefitinib or erlotinib, an acquired resistance to EGFR inhibitors, resulting in treatment failure, is associated with the development of an additional *EGFR* mutation.[6] The most extensively studied of such *EGFR* mutations occurs in exon 20, resulting in a substitution of methionine for threonine in codon 790 (T790M).[100-102] This mutation causes a change in the tridimensional structure of the tyrosine kinase domain and prevents both erlotinib and gefitinib from binding to EGFR.[103] According to a recent report, amplifi-

cation of the *MET* proto-oncogene could be involved in acquired resistance to EGFR tyrosine kinase inhibitors in patients with non–small-cell lung cancer.[104] *MET* amplification leads to EGFR-independent activation of the PI3K–AKT pathway through activation of HER3-dependent signaling. In a gefitinib-sensitive lung-cancer cell line that developed resistance to gefitinib as a result of *MET* amplification, inhibition of MET signaling restored sensitivity to gefitinib.[104] A pilot study of 18 tumor specimens from patients with non–small-cell lung cancer that had previously responded to gefitinib but that subsequently developed clinical resistance showed *MET* amplification in 4 of the tumors.[104]

FUTURE DIRECTIONS

Appropriate selection of patients is a major challenge for the clinical use of EGFR antagonists. In fact, although long-lasting therapeutic responses have been observed even in patients with heavily pretreated, metastatic cancer, responses are observed in only 10 to 20% of patients receiving these drugs.[105] Cancer cells must express functional EGFRs to respond to these agents. An optimal response to EGFR antagonists also requires the EGFR-activated intracellular signal-transduction machinery to be intact. In addition, EGFR-dependent cancer cells may escape from EGFR-targeted growth inhibition by using alternative growth factor receptor pathways or by constitutively activating downstream intracellular signaling effectors,[106-109] indicating the need for therapeutic strategies designed to overcome resistance to EGFR inhibitors.[110-112] Several molecular predictors have been detected for identifying patients who would be most likely to benefit from treatment with anti-EGFR drugs. However, most available clinical data are from retrospective studies and subgroup analyses; there is an urgent need to validate these observations in properly designed prospective studies. Another clinical issue is the need to determine the most effective sequences and combinations of EGFR inhibitors to use with chemotherapy, radiotherapy, or both in order to optimize cytotoxicity potentiation. In fact, the schedules that have been tested so far have been based on the empirical association of a standard chemotherapy regimen with the continuous administration of an EGFR-targeting drug rather than derived from molecular, pharmacokinetic, and pharmacodynamic studies.

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