Anti-EGFR Therapies: Clinical Experience in Colorectal, Lung, and Head and Neck Cancers

By Everett E. Vokes, MD [2] and Edward Chu, MD [3]

Anti-EGFR (epidermal growth factor receptor) therapies, including tyrosine kinase inhibitors (TKIs) and monoclonal antibodies, demonstrate activity in a variety of tumor types. While both inhibit the EGFR pathway, they act via different mechanisms.

The epidermal growth factor receptor (EGFR) regulates multiple cellular processes, including proliferation, differentiation, survival, motility, and blood vessel formation. Genetic alterations in the sequence of the EGFR gene or aberrations in the levels of protein expression may result in deregulation of EGFR function. Abnormally active EGFR may become an important contributor to oncogenic processes. The rationale for anti-EGFR therapies in cancer treatment relies on the role that EGFR may play in tumorigenesis and the frequent overexpression or hyperactivation of EGFR noted in many tumor types, including colorectal cancer (CRC), squamous cell carcinoma of the head and neck (SCCHN), and non-small-cell lung cancer (NSCLC). Overexpression of EGFR correlates with poor outcome and affects all aspects of carcinogenesis, including cell growth and invasion, angiogenesis, and metastasis.[1-4] In addition, the presence of activating mutations of EGFR may be common in malignant cells and correlates with neoplastic progression.[5]

Although tyrosine kinase inhibitors (TKIs) and monoclonal antibodies both inhibit EGFR signaling, their mechanisms of action fundamentally differ. Monoclonal antibodies bind specifically and with high affinity to the extracellular domain of the EGFR, competitively inhibiting binding of other growth factor ligands, including the epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α). Another important mechanism of action is antibody-receptor internalization; the EGFR disappears from the cell surface. This prevents ligand-induced autophosphorylation of the EGFR, interrupting the signaling cascade and leading to inhibition of cell growth, migration and metastases, and angiogenesis and induction of apoptosis.[6,7] Monoclonal antibodies may also activate immunologically mediated mechanisms, including antitumor-dependent cellular cytotoxicity and complement-mediated cytotoxicity, although the contribution of this activity to efficacy has not been conclusively demonstrated.[4] By contrast, TKIs bind to the catalytic domain of the EGFR within the cell to block the activation of downstream effectors.[1] Inhibition by TKIs may be either reversible or irreversible, depending on the type of molecule.[7]

Several phase II/III clinical trials have evaluated anti-EGFR therapy in various treatment settings. This article reviews the clinical activity of the TKIs and monoclonal antibodies in CRC, NSCLC, and SCCHN.

Clinical Experience in Metastatic Colorectal Cancer

Cetuximab

The majority of the clinical experience with anti-EGFR therapy in metastatic colorectal cancer has been conducted with the monoclonal antibody cetuximab (Erbitux); see Table 1. Phase II trials have shown activity of cetuximab as a single agent and in combination with both irinotecan (Camptosar)-and oxaliplatin (Eloxatin)-based chemotherapy in previously treated patients with metastatic colorectal cancer.[8,9,11,12] Results of a recent phase II trial also show the feasibility and activity of cetuximab plus bevacizumab (Avastin), with or without irinotecan, in patients with metastatic colorectal cancer who failed irinotecan, oxaliplatin, and fluoropyrimidines.[10]
A large, phase II randomized trial conducted by Cunningham et al.[8] showed impressive activity alone or in combination with irinotecan in patients with irinotecan-refractory disease. Enrolled patients had documented progression during or within 3 months following irinotecan-based therapy and immunohistochemical evidence of EGFR expression. Patients randomized to cetuximab plus irinotecan achieved an overall response rate of 23%; those treated with cetuximab alone achieved an overall response rate of 11%. The degree of EGFR expression, the number of prior therapies, and previous treatment with oxaliplatin did not affect the activity of study therapy. Treatment was generally well tolerated; the most commonly reported adverse event was skin toxicity. The incidences of diarrhea and neutropenia with irinotecan plus cetuximab were in the range that would be expected with irinotecan alone.

Importantly, the addition of cetuximab to chemotherapy showed modest response in patients who previously progressed on the same chemotherapy regimen, suggesting that addition of cetuximab may overcome treatment resistance in some patients.[8] Correlation of EGFR expression, as determined by immunohistochemistry, with clinical activity of cetuximab is inconsistent. In clinical
trials, the degree of EGFR expression as either percentage of cells staining positive or maximal staining intensity per cell did not correlate with response to cetuximab.[8,11] A retrospective analysis has also demonstrated that the activity of cetuximab is similar in both EGFR-negative and EGFR-positive patients, further highlighting the shortcomings of EGFR expression as a selection criterion.[16] A separate retrospective analysis, however, indicated a correlation between increased EGFR copy number as measured by fluorescence in situ hybridization (FISH) and response to anti-EGFR monoclonal antibodies.[17] Response to cetuximab is not dependent on the presence of EGFR mutations.[18]

Several clinical studies have examined whether cetuximab improves the efficacy of the first-line standard chemotherapy regimens FOLFOX ( fluorouracil [5-FU]/leucovorin/oxaliplatin) or FOLFIRI (5-FU/leucovorin/irinotecan) in patients with untreated metastatic colorectal cancer. An international phase II study (ACROBAT) has shown that cetuximab improves treatment outcomes when combined with FOLFOX-4 in colorectal cancer patients with untreated, EGFR-overexpressing stage IV disease.[19] Patients administered this combination achieved an overall response rate of 81%, which compares favorably to the 45% observed for FOLFOX-4 alone in the Intergroup 9741 trial.[20] An additional seven patients experienced stable disease, leading to an overall disease control rate of 98%—the highest reported to date in any clinical trial for advanced, metastatic colorectal cancer. The safety profile was tolerable, as the addition of cetuximab to FOLFOX-4 did not produce increases in diarrhea or neutropenia.

Clinical data also show the addition of cetuximab to FOLFIRI to be a safe and potentially efficacious first-line regimen for metastatic colorectal cancer. The feasibility of this combination was first demonstrated in two early-phase clinical studies that showed that cetuximab plus FOLFIRI is active and tolerable as first-line therapy in patients with EGFR-positive metastatic colorectal cancer.[21,22] In addition to these initial promising results, a second phase II study has also shown efficacy for cetuximab with FOLFIRI in this setting.[23] Patients with untreated, EGFR-positive disease achieved response and disease control rates of 43% and 88%, respectively. The addition of cetuximab did not exacerbate the safety profile of FOLFIRI.

Based on these promising results, clinical studies are ongoing to evaluate cetuximab in combination with FOLFOX or FOLFIRI in previously untreated patients with metastatic colorectal cancer. A phase II trial is ongoing to determine the efficacy of cetuximab in combination with FOLFOX-4 as first-line therapy in this setting.[24] The Cancer and Leukemia Group B (CALGB) is conducting a phase III study to compare the FOLFOX-4 and FOLFIRI regimens with or without cetuximab. A second ongoing phase III study, CRYSTAL, is evaluating the efficacy of cetuximab in combination with FOLFIRI in previously untreated patients with EGFR-overexpressing disease.

Tyrosine Kinase Inhibitors

Results of three phase II trials of TKIs in colorectal cancer are available (Table 1). Fisher and colleagues evaluated FOLFOX-4 plus gefitinib (Iressa) in previously treated or untreated patients with advanced colorectal cancer. Previously untreated patients achieved an overall response rate of 77%; previously treated patients achieved an overall response rate of 29%. Treatment resulted in considerable grade 3/4 toxicities, including diarrhea (54%), neutropenia (52%), and vomiting (22%), which were all reported at higher incidences than typically associated with FOLFOX-4 alone.[13] A smaller phase II trial of 5-FU/leucovorin/irinotecan plus gefitinib in previously treated patients with advanced colorectal cancer showed minimal activity, with dose-limiting neutropenia and dehydration/metabolic abnormalities.[14] A trial of single-agent erlotinib (Tarceva) in advanced colorectal cancer patients previously treated with irinotecan or 5-FU reported no objective responses.[15]

Clinical Experience in Advanced NSCLC

Cetuximab

Results from two clinical studies show the feasibility and activity of cetuximab plus cisplatin/vinorelbine or paclitaxel/carboplatin in previously untreated patients with EGFR-positive advanced NSCLC (Table 2). In a phase II study by Rosell and colleagues,[25] patients with EGFR-positive disease were randomized to treatment with cisplatin/vinorelbine with or without cetuximab. Treatment with combination chemotherapy plus cetuximab resulted in an overall response rate of 32%, compared with 20% with chemotherapy alone. Toxicity was similar in the two treatment arms, demonstrating the safety of adding cetuximab to chemotherapy, with enhanced activity in this treatment setting.
### Clinical Experience in Advanced Non–Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients (N)</th>
<th>Regimen</th>
<th>OR</th>
<th>MS</th>
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<th>Grade 3/4 Toxicities</th>
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<tr>
<td><strong>Cetuximab</strong></td>
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<tr>
<td>Rosell et al [25] Phase II</td>
<td>Previously untreated advanced NSCLC, EGFR+ (86)</td>
<td>Cisplatin/ vinorelbine + cetuximab</td>
<td>32%</td>
<td>NR</td>
<td>4.7 mo</td>
<td>Leukopenia (64%), nausea/vomiting (17%), asthenia/fatigue (17%), infection (12%), fever/chills (10%), thrombocytopenia (7%), rash (5%), diarrhea (2%)</td>
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<td>Cisplatin/ vinorelbine</td>
<td>20%</td>
<td>NR</td>
<td>4.2 mo</td>
<td>Leukopenia (51%), nausea/vomiting (14%), asthenia/fatigue (2%), infection (5%), fever/chills (7%), thrombocytopenia (5%)</td>
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<td>Thienelt et al [26] Phase III</td>
<td>Previously untreated stage IV NSCLC, EGFR+ (31)</td>
<td>Carboplatin/ paclitaxel + cetuximab</td>
<td>26%</td>
<td>11 mo</td>
<td>5 mo</td>
<td>Fatigue (23%), leukopenia/neutropenia (4%), myalgia/arthritis (16%), rash (13%), neuropathy (10%), pulmonary embolus (9.7%), nausea/vomiting (7%), hypersensitivity (3%)</td>
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<th>TKIs</th>
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<td>iDEAL [27] Randomized phase II</td>
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<td>HD: 1% CR</td>
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<td>IDEAL 2 [28] Randomized phase II</td>
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<td>HD: 9% PR</td>
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<td>INTACT 1 [29] Phase III</td>
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<td>HD: 2% CR</td>
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<td>Gemcitabine/ cisplatin alone</td>
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<td>INTACT 2 [30] Phase III</td>
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<tr>
<td>HD: 30% (inc. 1% CR)</td>
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<td>Paclitaxel/ carboplatin</td>
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A phase I/II study has also shown activity for cetuximab in combination with chemotherapy in this setting. Patients with previously untreated metastatic NSCLC with EGFR-positive disease who received a regimen of cetuximab with carboplatin and paclitaxel achieved an overall response rate of 29%, with an additional 36% of patients experiencing stable disease. Median survival reached 11 months. Toxicity, the primary end point of the study, was tolerable, with myalgia, arthralgia, neutropenia, and rash the most clinically relevant adverse events.[26] Collectively, these studies demonstrate that the addition of cetuximab to platinum-based chemotherapy is feasible for the treatment of advanced NSCLC.

Tyrosine Kinase Inhibitors
The majority of clinical experience with TKIs has been in patients with NSCLC (Table 2). While gefitinib demonstrated modest activity as a single agent in randomized phase II trials (IDEAL 1 and 2) in previously treated patients with advanced NSCLC,[27,28] phase III trials (INTACT 1 and 2) failed to show a benefit with the addition of gefitinib to chemotherapy in previously untreated patients with advanced disease.[29,30]

A randomized trial comparing erlotinib with best supportive care conducted by the National Cancer Institute of Canada demonstrated activity of erlotinib as a single agent in pretreated patients, with significantly increased survival, progression-free survival, and response rates.[31] Benefit extended across most subgroups, with logistic-regression analysis confirming that nonsmokers, the presence of adenocarcinoma, and EGFR expression were associated with a response to erlotinib. A univariate analysis of patients with NSCLC who had received erlotinib therapy revealed that EGFR expression or polysomy, but not EGFR mutations, was associated with significantly improved responsiveness. In a multivariate analysis, EGFR expression, polysomy, or mutation was not associated with increased survival after erlotinib treatment.[34] A similar trial with gefitinib produced similar clinical trends but failed to achieve statistical significance.[35]

As with gefitinib, trials of erlotinib in combination with chemotherapy (TALENT and TRIBUTE) yielded negative results.[32,33] Thus, TKIs may have a role as monotherapy in the second- or third-line setting for patients with NSCLC. It may also be feasible to combine TKIs with bevacizumab for later-line treatment of NSCLC. However, for patients with newly diagnosed NSCLC, combination chemotherapy remains the standard of care.[36]

Response to TKIs varies by patient population. Women, patients with adenocarcinoma, nonsmokers, and Asians appear more sensitive to treatment.[34] In addition, studies conducted on tumor tissue samples have identified mutations that may predict response to gefitinib[37,38], and these
mutations may be more common among populations showing increased sensitivity to gefitinib. In fact, these mutations may account for the majority of responses to gefitinib reported in clinical trials.[38] Results of studies at the University of Colorado suggest that an increased level of gene copies determined by FISH or high expression detected by immunohistochemistry as well as the presence of EGFR mutations may predict response to gefitinib in patients with NSCLC.[39-43] In contrast, clinical results indicate that erlotinib response correlates with EGFR expression, but not with the presence of mutations.[34] Nonetheless, some evidence suggests that specific protein expression patterns correlate with response to erlotinib,[44] and nonsmokers treated with erlotinib appear to benefit more from treatment than smokers.[45] The CALGB is conducting a randomized phase II trial (CALGB-30406) to evaluate erlotinib alone or in combination with chemotherapy in an enriched population of nonsmokers to determine if there is a benefit to combined therapy in this population. This hypothesis is supported by the results from TRIBUTE, in which improved survival rates were observed for nonsmokers given erlotinib in combination with chemotherapy for the treatment of advanced NSCLC.[32]

Clinical Experience in Head and Neck Cancer

Cetuximab

Several randomized phase III trials and large phase II trials show promising activity of cetuximab in SCCHN (Table 3). A phase III international clinical trial demonstrated that the addition of cetuximab to radiotherapy is feasible and results in nearly double survival times in patients with locally advanced head and neck cancer without significantly exacerbating common radiation-associated toxicities. The trial enrolled 424 patients with locoregionally advanced squamous cell cancer of the oropharynx, hypopharynx, or larynx. Patients were stratified by performance status, tumor stage, involved lymph nodes, and radiation fractionation regimen.
Treatment with cetuximab plus radiotherapy conferred a statistically significant survival advantage over radiotherapy alone (median survival: 54 vs 28 months, respectively; P = .02). The toxicity profile was similar in both treatment arms and consisted mainly of toxicities associated with high-dose radiotherapy in this treatment setting; however, some increased skin toxicity was reported with combination cetuximab plus radiotherapy.[46]

Another phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG) showed that cetuximab plus chemotherapy increased response over chemotherapy alone in recurrent head and neck cancer. Patients with recurrent or metastatic SCCHN were randomized to cisplatin plus cetuximab or cisplatin alone. Combination therapy resulted in significantly improved response compared with chemotherapy alone (26% vs 10%, respectively; P = .029); however, differences in survival (4.2 vs 2.7 months, respectively) did not reach statistical significance. The safety profile was similar in the two treatment arms, with increased incidences of rash and hypersensitivity reaction the most clinically relevant cetuximab-related adverse events reported in the combination arm.[47]

As demonstrated in a phase II trial, cetuximab may be a valuable therapeutic option for patients with...
platinum-resistant advanced SCCHN. In this study, patients with platinum-refractory recurrent/metastatic SCCHN given cetuximab as monotherapy achieved an overall response rate of 12.6%. In addition, disease stability was reported in 33% of patients, leading to a disease control rate of 45.6%. The safety profile was tolerable, with reversible moderate skin rash the most clinically relevant toxicity.[48]

Response to cetuximab in combination with chemotherapy has also been demonstrated in two phase II trials in patients who previously progressed on the same chemotherapy regimen.[49,50] Current research is evaluating the use of cetuximab in combination with bevacizumab (National Cancer Institute [NCI]-6588) or chemoradiotherapy (ECOG-3303, ECOG-2303, and Radiation Therapy Oncology Group [RTOG]-0234) in head and neck cancer.

The promising results of the phase III trial of cetuximab in combination with radiotherapy may indicate the potential to obtain results comparable to more toxic concurrent chemoradiotherapy regimens. Recommended treatments for unresectable SCCHN or recurrent disease not previously treated with radiotherapy depend on the performance status of the patient. For patients with good performance status, the current standard treatment is concurrent platinum-based chemotherapy and radiotherapy, while patients with fair performance status can be administered induction chemotherapy followed by radiotherapy or radiotherapy alone if organ preservation is a goal or the patient is inoperable.[53] Combination chemoradiotherapy with cisplatin-based therapy yields 2-year survival rate of 68% and 3-year overall survival rates of 37% to 55% in this population.[54-57] Phase III trials investigating this question are ongoing. For patients with recurrent disease, doublet chemotherapy remains the standard approach.

Tyrosine Kinase Inhibitors

Smaller phase II trials have investigated the use of TKIs in previously treated or untreated patients with advanced head and neck cancer.[51,52] Results of a phase II trial of induction chemotherapy followed by gefitinib plus chemoradiotherapy in previously untreated advanced head and neck cancer indicate promising activity. An overall response rate of 88% was reported; however, treatment resulted in substantial grade 3/4 mucositis and dermatitis.[51]

Phase II studies have also demonstrated modest single-agent efficacy for gefitinib when given to patients with recurrent and/or metastatic disease. Cohen and colleagues have reported that SCCHN patients achieved an overall response rate of 11% when administered a 500-mg daily dose of gefitinib. However, a second phase II study evaluating 250-mg daily gefitinib revealed only modest activity at this reduced dose. A 1.4% overall response rate was observed, with median progression-free survival and overall survival rates of 1.8 and 5.5 months, respectively. The investigators concluded that a dose-response relationship possibly exists for gefitinib in SCCHN.[58,59]

Similarly, a phase II study has shown modest activity for single-agent erlotinib in patients with recurrent or metastatic SCCHN. Patients enrolled in this study achieved an objective response rate of 4.3%, and disease stabilization was maintained in 38.3% of patients for a median duration of 16.1 weeks.[52] A recent phase I study evaluating erlotinib with bevacizumab has also shown efficacy in this setting. Patients with recurrent or metastatic SCCHN administered this combination achieved an overall response rate of 14.6%, with two complete responses reported. In addition, the safety profile for erlotinib with bevacizumab was consistent with the administration of each agent as monotherapy, with no synergistic toxicity reported.

Responses to TKIs do not appear to be linked to EGFR mutation in SCCHN patients. A recent study screened for mutations in EGFR as well as in the HER2 gene ErbB2 using tumor specimens from SCCHN patients who were administered TKI therapy. Although EGFR mutations were not identified in any specimens from responders to TKI therapy, a single responsive case harbored a mutation within exon 20 of ErbB2. The investigators concluded EGFR mutations are not linked to TKI response in SCCHN. However, responses to TKI may rely on alternative mechanisms, including mutations in ErbB2.[60]

The activity profile of TKIs in SCCHN may be different from that in NSCLC. There may be a dose-response curve in head and neck cancer that is not seen in NSCLC, and, to date, no mutations predicting response in head and neck cancer have been identified.[61] Use of TKIs in SCCHN continues with phase I/II trials of erlotinib alone (Johns Hopkins Oncology Center [JHOC]-J0384) or in combination with bevacizumab (NCI-6488), chemotherapy (ID02-668 and Ohio State University [OSU]-0213), or chemoradiotherapy (National Cancer Institute of Canada [CAN-NCIC]-HN5, 2003-1049, JHOC- 20020723, and Case Western Reserve University [CWRU]-1301).

Overview of the Therapeutic Profile of Anti-EGFR Therapy

Anti-EGFR therapy is generally well tolerated, particularly when compared with cytotoxic
Chemotherapy. Specifically, these targeted therapies are nearly devoid of the hematologic toxicities noted with cytotoxics. This lack of overlapping toxicities provides a strong rationale for combining anti-EGFR therapy with cytotoxic chemotherapy and other therapies. The primary toxicities of anti-EGFR therapy are discussed in detail in other articles of this supplement.

Rash is common and frequently mild to moderate, but may be severe.[1,62] Diarrhea is generally mild to moderate with monoclonal antibodies, but may be dose-limiting with TKIs.[63] Hypersensitivity reactions with monoclonal antibodies are rarely severe, and incidence may vary depending on how much mouse protein is part of the IgG backbone (chimeric vs humanized vs fully human antibodies).[1]

As targeted biologic agents, anti-EGFR therapies provide a treatment alternative for patients who cannot tolerate or who are otherwise ineligible for chemotherapy. Anti-EGFR therapy offers an important treatment benefit in refractory disease. Evidence suggests that monoclonal antibodies may circumvent tumor resistance to chemotherapy. Several trials demonstrated response to cetuximab in combination with chemotherapy in patients who previously progressed on the same chemotherapy regimen.[8,10,49,50] In addition, anti-EGFR therapies maintain activity in heavily pretreated populations.[8-11,13,27,28,31,47-50,52] In contrast to cytotoxic chemotherapy, the clinical activity of single-agent anti-EGFR therapies appears to remain consistent and less dependent on the extent of prior therapy.

The activity observed with anti-EGFR therapies in previously treated patients may indicate a potential role in earlier-stage disease, as debulking treatment in patients with initially unresectable disease to allow more extensive resection.

Ongoing Development of Anti-EGFR Therapies

Ongoing trials continue to investigate the use of cetuximab in combination with chemotherapy and other biologics in patients with colorectal cancer. The BOND trials are comparing cetuximab/irinotecan vs cetuximab alone (BOND 1) and cetuximab/bevacizumab with or without irinotecan in bevacizumab-naive (BOND 2) and bevacizumab-refractory (BOND 3) patients.[10] In the Southwest Oncology Group (SWOG)/CALGB GI Intergroup phase III randomized trial, patients are allowed to receive either FOLFOX or FOLFIRI as their first-line regimen and then are randomized to receive either bevacizumab, cetuximab, or the combination of bevacizumab/cetuximab. An ongoing trial (SWOG-0342) is investigating concurrent vs sequential treatment with cetuximab and paclitaxel/carboplatin chemotherapy in NSCLC.

Current research is focusing on the following issues to further develop the role of anti-EGFR antibodies in cancer:

• Which patient populations will benefit most from treatment? Identifying biomarkers predictive of response remains a research priority.
• Can increased doses of monoclonal antibodies, such as cetuximab, improve treatment outcomes in patients with chemoresistant disease? An ongoing European trial, EVEREST, is addressing this issue by comparing the safety and efficacy of cetuximab (fixed dose vs escalating doses) in patients with irinotecan-resistant EGFR-positive metastatic colorectal cancer. Response, time to progression, and survival correlate with the presence and severity of skin reactions in some tumor types, suggesting that development of rash may be an important clinical indicator of outcome.[8,9,49] Titrating dose to development of a severe rash might improve clinical outcome.
• What role will cetuximab plus irinotecan- or oxaliplatin-based chemotherapy have in first-line treatment of colorectal cancer?
• What is the optimal scheduling of cetuximab? Ongoing European trials are currently investigating an every-2-week schedule.

Other anti-EGFR monoclonal antibodies are at earlier stages of clinical development. Panitumumab (ABX-EGF), a fully human monoclonal antibody, shows activity as a single agent in colorectal cancer and other solid tumors and in combination with chemotherapy in NSCLC.[64-66] Matuzumab (EMD-72000), a humanized monoclonal antibody, has shown activity alone or in combination with chemotherapy in a variety of tumor types, including colorectal cancer.[67-71] Clinical development of the TKIs continues with several clinical trials being conducted in various treatment settings. Ongoing trials of gefitinib include the following:

• Phase II and III trials of gefitinib alone or in combination with chemotherapy in SCCHN and NSCLC (NCT-00072878, ECOG-E1302, NCI-1701, NCT-00076388, European Organisation for Research and Treatment of Cancer [EORTC]-08021, and SWS-SAKK-19/03)
• Phase II trial of induction gefitinib followed by surgery or radiotherapy in SCCHN (NCI-6012)
• Phase I trials of gefitinib plus chemoradiotherapy in SCCHN (NCI-4551 and NCI-5926)
• Phase II pilot trial of neoadjuvant gefitinib in resectable NSCLC (Moffitt Cancer Center [MCC]-13922)
• Phase I/II trials of gefitinib in combination with other biologics in NSCLC (Memorial Sloan Kettering Cancer Center [MSKCC]-1700)

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Cancer Center [MSKCC]-04033, UCLA-0407057, and others)
• Trials in other tumor types, including breast and renal cancers.

Ongoing trials of erlotinib include the following:
• Phase III trial of erlotinib plus chemotherapy with whole brain irradiation and stereotactic radiosurgery in NSCLC with brain metastases (RTOG-0320)
• Phase I/II trials of erlotinib plus chemotherapy in SCCHN (NCI-5393) or NSCLC (CALGB-30406)
• Phase I/II trial of single-agent erlotinib in NSCLC, SCCHN, and ovarian cancer (NCI-5948)
• Phase I/II trials of erlotinib in combination with other biologics with or without chemotherapy in various tumor types, including colorectal cancer and NSCLC (NCI-6588, North American Brain Tumor Consortium [NABTC]-0402, and others)
• Trials in other tumor types

Conclusion
A growing body of evidence supports the continuing investigation of anti-EGFR therapy in various tumor types. Clinical experience to date shows modest activity as single agents and moderate activity in combination regimens in metastatic CRC, SCCHN, and NSCLC. The trials summarized herein demonstrate the safety and feasibility of anti-EGFR therapy in combination with chemotherapy, radiotherapy, and other biologic therapy in several treatment settings. Anti-EGFR therapies, including both TKIs and monoclonal antibodies, yield consistent activity regardless of prior therapy, increasing their usefulness in patients with disease refractory to chemotherapy. In addition, their tolerable safety profiles make anti-EGFR therapies appropriate for patients who cannot tolerate chemotherapy.[8-11,13-15, 25, 27-33,46-52]

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