Epidermal Growth Factor Receptor Inhibitors: Coming of Age
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Background: Agents targeting the epidermal growth factor (EGFR)-mediated signaling pathway are used in the treatment of various solid tumors, including lung, breast, pancreatic, colorectal, and head and neck cancers.

Methods: Clinical evidence supporting the benefits of targeted agents directed against EGFR/HER1 in various solid tumors is discussed, as well as the survival end points used in the pivotal clinical trials, current applications, and future research directions. Agents reviewed include the monoclonal antibodies cetuximab and panitumumab, both of which block ligand binding to the extracellular domain, and the small-molecule tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib that exert their effects at the intracellular portion of the receptor to prevent tyrosine kinase phosphorylation and the activation of signal transduction pathways.

Results: EGFR inhibitors have a mechanism of action distinct from traditional cytotoxic therapies, and combining these agents with chemotherapy produces synergistic anticancer activity without overlapping toxicity profiles. The level of EGFR expression does not correlate with agent response, and many tumors are resistant to treatment. Even if tumors are initially sensitive to these agents, they inevitably acquire resistance through complex, poorly understood molecular mechanisms.

Conclusions: EGFR-directed therapies have changed the treatment paradigms in metastatic lung, colorectal, and head and neck cancers and improved outcomes. A better understanding of mechanisms of resistance to these agents is crucial for effective drug development. Predictive biomarkers are being developed to deliver personalized therapies.

Introduction
The epidermal growth factor receptor (EGFR) family is a group of receptor tyrosine kinases that mediates cell proliferation, survival, migration, and differentiation. The EGFR family consists of 4 members: ERBB1/EGFR, ERBB2 (formerly HER2/neu), ERBB3 (formerly HER3), and ERBB4. The structure of these receptor tyrosine kinases spans from outside of the cell through the plasma membrane and into the cytoplasm where enzymatic activity can be mediated through linear as well as horizontal interactions. These proteins are inactive as single subunits and must be activated by ligands to form homodimers or heterodimers to translate extracellular signals into intracellular activity.

In multiple tumor types, including head and neck, lung, breast, and colorectal cancers, this family of receptor tyrosine kinases has been found to be deregulated, thus leading to an overexpression and amplification of EGFR and ensuing inappropriate cellular stimulation. Receptor overexpression has been correlated with a more aggressive clinical course in multiple tumor types. Given the nature of this pathway in tumor development and proliferation, efforts have been directed at anti-EGFR therapies. The most developed anti-EGFR therapies include monoclonal antibodies, which target the extracellular domain, and the small-molecule tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib that exert their effects at the intracellular portion of the receptor to prevent tyrosine kinase phosphorylation and the activation of signal transduction pathways.

Lung Cancer
Cetuximab, an anti-EGFR immunoglobulin (Ig) G1 chimeric monoclonal antibody, was assessed in combination with chemotherapy in patients with EGFR-expressing non–small-cell lung cancer (NSCLC). Compared with patients assigned to chemotherapy alone, those in the cetuximab group had longer median survival rates (11.3 months vs 10.1 months; P = .044) but a higher incidence of adverse events, including febrile neutropenia, acne-like rash, diarrhea, and infusion-related reactions. Higher EGFR expression was associated with improved survival rates in the cetuximab group.


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Due to this relatively small benefit with significantly increased toxicities, cetuximab has not been approved in the United States or Europe for NSCLC.

Gefitinib was the first drug developed as an inhibitor of the EGFR tyrosine kinase domain. Gefitinib reversibly competes with adenosine triphosphate for binding to the intracellular domain of EGFR tyrosine kinase and prevents EGFR phosphorylation and downstream signaling. It was initially evaluated in a phase II trial that cited evidence of the drug’s activity in Japanese patients with advanced NSCLC who had been previously treated. Subsequent trials in Europe and the United States showed less activity against disease than what was seen in Japan, but the patient cohort of young women of East Asian descent who never-smokers appeared to respond at greater rates. Further work revealed that this cohort had an increased rate of EGFR mutations primarily located on exons 19 (deletion) and 21 (mutation). Based on early trials, gefitinib was initially approved by the US Food and Drug Administration (FDA) in 2003.

In a subsequent placebo-controlled phase III trial, the Iressa Survival Evaluation in Lung Cancer study, no survival advantage with gefitinib was reported in patients with unselected NSCLC. Survival benefit was seen in patients of Asian origin and nonsmokers. The FDA rescinded approval of the drug in 2005 secondary to a lack of benefit compared with placebo in an unselected population. The largest study of gefitinib was the IRESSA Pan-Asia Study trial, which compared the drug to conventional chemotherapy in unselected patients with advanced NSCLC and found improved progression-free survival (PFS) but no difference in overall survival (OS). A subgroup analysis of patients with EGFR mutations demonstrated improvement in PFS (hazard ratio [HR] = 0.48; 95% confidence interval [CI], 0.36–0.64). No statistically significant difference in survival was seen, but patients in the gefitinib arm were favored. Furthermore, in patients without the EGFR mutation, a detrimental effect was seen with gefitinib (HR for PFS = 2.85). Based on these findings, a phase III trial was conducted in Japan among patients with EGFR mutations that compared gefitinib with combination cisplatin/docetaxel. Median PFS combination rates were significantly longer in the gefitinib arm compared with the chemotherapy arm (9.2 vs 6.3 months). Gefitinib is currently available in Europe and Asia.

Erlotinib is another reversible TKI and is similar to gefitinib. The difference in the mechanism of the 2 drugs is poorly understood but could be from a more rapid hepatic clearance of gefitinib. The role of erlotinib in refractory NSCLC was evaluated in a randomized placebo-controlled, phase III BR.21 trial conducted in Canada. OS rates were significantly higher in the erlotinib group, with a median survival of 6.7 months compared with 4.7 months in the placebo group (HR = 0.70). Responses were more common in women, in patients with adenocarcinoma, and in patients who did not smoke. By contrast to prior reports, response rates were higher in patients with EGFR-expressing tumors. No significant difference in response rate was observed by EGFR mutation status (16% vs 7%; ). Based on these trial results, the FDA approved the use of erlotinib in refractory NSCLC in 2004.

Subsequently, erlotinib was compared with conventional chemotherapy in treatment-naive patients with advanced NSCLC who harbored the EGFR mutation (exon 19 deletion or L858R mutation in exon 21) in 2 large trials, EURTAC and OPTIMAL. Significant improvements in PFS were reported in both trials. However, survival differences were not observed, presumably because of the crossover design. Patients in the erlotinib group of the OPTIMAL trial experienced better quality of life compared with those in the chemotherapy group. The utility of erlotinib as a maintenance therapy was assessed in a phase III, placebo-controlled study. Patients who had not progressed after receiving chemotherapy were randomized to either erlotinib or placebo. The OS rates were significantly prolonged in this unselected population. Benefit was seen irrespective of EGFR mutation status; however,
patients with an EGFR mutation had improved PFS (HR = 0.10; 95% CI, 0.04–0.25). In the ATLAS trial, the addition of erlotinib to maintenance bevacizumab therapy resulted in improved outcomes. Preclinical models suggest that erlotinib may improve the cytotoxic effects of chemotherapy. Several phase III trials were conducted to improve the outcomes of patients with advanced NSCLC undergoing chemotherapy by adding gefitinib or erlotinib to therapy. However, no differences in clinical outcomes were observed with combination EGFR TKI and chemotherapy. One possible explanation for the failure to demonstrate a survival advantage in this combination could be secondary to the inclusion of unselected patients regardless of their EGFR mutation status. Prior studies have demonstrated that the benefits of gefitinib and erlotinib are primarily restricted to patients with EGFR-mutated tumors. Another explanation is that a negative interaction may exist between EGFR TKIs and chemotherapy when they are concurrently administered. EGFR TKIs result in G1 cell-cycle arrest that may potentially interfere with the cell-cycle specific (S and G2/M phase) cytotoxic effect of chemotherapy. Thus, currently, erlotinib and gefitinib cannot be recommended as concomitant treatment to chemotherapy.

Afatinib is a novel, irreversible TKI with dual specificity for ERBB1 and ERBB2. It was found to have activity in preclinical models with the exon 20 gatekeeper T790 mutation, which is present in more than one-half of patients with acquired resistance to TKIs. Afatinib improved PFS rates in patients with NSCLC who had previously progressed on erlotinib or gefitinib. Results of a phase III trial comparing afatinib with chemotherapy in patients with an EGFR mutation were reported at the 2012 annual meeting of the American Society of Clinical Oncology. An improvement in PFS of 4.2 months was observed, but OS data were still immature. The FDA recently granted approval for the use of afatinib in patients with EGFR-mutated NSCLC along with companion diagnostic testing for EGFR mutations.

Based on current consensus guidelines, EGFR mutations should be tested in newly diagnosed patients with advanced NSCLC. This testing can be performed via polymerase chain reaction for the selected mutations (exons 18, 19, and 21) in a laboratory that abides by the Clinical Laboratory Improvement Amendments. Although this allows for information only on prespecified alleles, it is more rapid and cost-effective than direct sequencing or next generation sequencing. Resistance to TKIs despite EGFR mutation has recently been described. Mechanisms of secondary resistance, which are thought to occur downstream of the target of the drug, have been hypothesized. Primary and secondary resistances have been associated with the T790M mutation, indicating a clinical course similar to wild-type EGFR. Current recommendations endorse routine testing for EGFR mutations in patients with advanced NSCLC, especially those likely to harbor the mutation (young patients, women, never-smokers, and those of Asian descent). Patients with the EGFR mutation who have metastatic disease should be started on TKIs in the first-line setting. However, it is not yet known when and if patients should be transitioned to cytotoxic chemotherapy or how to treat resistant disease. Future studies may help to answer these questions.

**Colorectal Cancer**

EGFR expression has been associated with malignant transformation as well as worse clinical outcome in colorectal cancer (CRC). Based on their activity in lung cancer, the TKIs erlotinib and gefitinib have been studied in phase II trials in CRC. Minimal effect was seen when these TKIs were studied as single agents. Combining TKIs with standard chemotherapy also did not show a significant benefit and was associated with increased toxicities. Monoclonal antibodies have demonstrated more encouraging results. Single-agent cetuximab has been associated with an improvement in a median OS of 1.5 months in refractory patients with CRC. Subsequent analysis demonstrated that survival benefit was limited to patients with wild-type Kirsten rat sarcoma (K-ras) tumors. Combination cetuximab/irinotecan therapy in patients with irinotecan-refractory CRC resulted in improved response and PFS, with no significant difference in OS. This lack of difference in OS was thought to be secondary to crossover design. Patients with higher severity of rash derived more benefit. These results led to the FDA approval of cetuximab for metastatic CRC.

The next step in the development of anti-EGFR antibodies for CRC was the assessment of their activity in combination with standard chemotherapy in earlier lines of therapies. In the CRYSTAL trial, cetuximab, in addition to 5-fluorouracil (5-FU)/leucovorin/irinotecan chemotherapy, was compared with 5-FU/leucovorin/irinotecan alone in patients with metastatic CRC who were naive to chemotherapy. PFS marginally improved, but no difference was seen in OS. A subsequent analysis demonstrated that the benefit of cetuximab was limited to patients with wild-type K-ras tumors with a 3.5-month improvement in OS. In patients with mutant K-ras tumors, cetuximab had a detrimental effect. Similar results were seen in the OPUS trial, which assessed the role of cetuximab in combination with 5-FU/leucovorin/oxaliplatin chemotherapy. However, the survival improvement did not reach statistical significance in patients with wild-type K-ras tumors, presumably due to small sample size.
By contrast, the NORDIC-VII trial, which assessed combination cetuximab/bolus 5-FU/leucovorin/irinotecan did not demonstrate any difference in PFS regardless of K-ras mutation status.66 In the unselected population, the median PFS in the experimental group was 8.3 months vs 7.9 months in the control group (wild-type K-ras median PFS = 7.9 months vs 8.7 months). In patients with K-ras–mutant tumors, a trend was seen toward an increase in PFS in the cetuximab group, with a median PFS of 9.2 months vs 7.8 months, but this did not reach statistical significance ($P = .07$). Bolus 5-FU instead of standard infusional 5-FU was used in this trial, which is the standard of care in the United States. A large phase III COIN trial of 1,630 patients conducted in the United Kingdom evaluated the addition of panitumumab to fluoropyrimidine and oxaliplatin as first-line therapy.37 The choice of fluoropyrimidine, 5-FU, or capecitabine was based on patient and physician preferences, with the majority of patients receiving capecitabine. K-ras mutation status was prospectively evaluated in contrast to most of the previous trials. No differences in survival or PFS were reported in the unselected, wild-type K-ras and K-ras mutant groups. Among patients with wild-type K-ras tumor types receiving 5-FU–based treatment, the PFS was prolonged in the cetuximab group (HR = 0.72; 95% CI, 0.53–0.98). Frequent dose reductions and interruptions were reported, particularly in the patients receiving cetuximab. Further, the median OS of 17.9 months in the cetuximab arm and 17 months in the control group was lower than that seen in first-line CRC therapy trials.40–42

Panitumumab is a fully human monoclonal IgG2 antibody that has similar efficacy and adverse events compared to cetuximab. A randomized, placebo-controlled, phase III trial in patients with refractory CRC revealed that panitumumab use was associated with improved PFS.48 The results from this study led to FDA approval of the drug in 2006. Panitumumab was evaluated as a first-line therapy in combination with leucovorin/5-FU/oxaliplatin chemotherapy in the randomized phase III PRIME trial.49 Similar to prior studies, benefit was restricted to patients harboring wild-type K-ras tumor with improvement in PFS and a nonstatistical significant improvement in OS. In a phase III trial, panitumumab in addition to leucovorin/5-FU/irinotecan as a second-line therapy improved PFS in patients with wild-type K-ras tumors.50

Based on the activity of anti-EGFR agents and the vascular endothelial growth factor antibody bevacizumab, in combination with chemotherapy for metastatic CRC, randomized trials were conducted to evaluate if anti-EGFR agents in addition to chemotherapy and bevacizumab would further improve outcomes. A pilot phase II BOND-2 trial assessed the dual antibody therapy, cetuximab and bevacizumab, alone or in conjunction with irinotecan.51 Response rates, time to progression, and OS were more favorable in the experimental group. Results of this study led to larger randomized trials. CAIRO-2 was a phase III trial of 755 patients that evaluated the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab as first-line treatment in patients with metastatic CRC.52 No differences in PFS or OS rates were observed in the unselected or wild-type K-ras tumor group. Patients with K-ras–mutated tumors had worse outcomes if they received cetuximab. Similar results were seen with PACCE study, which evaluated the combination of panitumumab, bevacizumab, and chemotherapy.53 The addition of anti-EGFR antibody not only failed to improve outcomes, but also led to inferior PFS and OS, regardless of K-ras mutation status. Thus, no role exists for dual antibody therapy in the treatment of CRC.54

The results of prior studies suggest that (1) anti-EGFR antibodies have activity only in wild-type K-ras CRC, (2) cetuximab and panitumumab may be interchangeably used, (3) cetuximab and panitumumab activity is present in any line of therapy in combination with chemotherapy, (4) no role exists for anti-EGFR antibodies in the adjuvant setting, and (5) the backbone of chemotherapy may have a differential effect on the activity of these agents.55,56 The National Comprehensive Cancer Network guidelines suggest that cetuximab should not be combined with oxaliplatin, but the guidelines do permit the use of combination panitumumab/oxaliplatin.57 One possible explanation for the negative results seen in the NORDIC and COIN trials could be that bolus 5-FU and capecitabine, respectively, were utilized instead of infusional 5-FU. Further, no advantage exists for the addition of bevacizumab to combination anti-EGFR antibody/chemotherapy.52,54

Head and Neck Cancers

In a randomized phase III trial, cetuximab was added to radiotherapy for locally advanced disease and was associated with improvements in response, PFS, and OS.58 Combination cetuximab/cisplatin has been tested in patients with metastatic head and neck cancers. A randomized controlled trial of cetuximab/cisplatin compared with cisplatin alone demonstrated an improved response rate, with no significant difference in OS, presumably due to small sample size.59 A larger randomized phase III trial demonstrated that the addition of cetuximab to 5-FU and platinum chemotherapy resulted in an improvement in median OS by 2.7 months.60 Cetuximab was approved by FDA in 2006 for use in locally advanced, recurrent, and metastatic head and neck cancers.

Among the TKIs, gefitinib has not been shown to be effective and has been associated with an increased
risk for hemorrhage. Although phase II data showed some activity of erlotinib in metastatic head and neck cancers, this was not supported in further studies.\textsuperscript{52}

**Pancreatic Cancer**

EGFR is overexpressed in pancreatic cancer, and EGFR overexpression has been associated with a poor prognosis.\textsuperscript{63,64} Based on preclinical activity and encouraging phase II trial results, a randomized phase III trial evaluated the role of cetuximab in addition to gemcitabine.\textsuperscript{65} No differences in any of the clinical outcomes were noted. By contrast, another phase III trial comparing gemcitabine/erlotinib with gemcitabine alone demonstrated a small but significant improvement in survival (HR = 0.82; 95% CI, 0.69–0.99).\textsuperscript{66} Despite the fact that the median OS was increased by only 2 weeks, this trial was notable because it has been the only study to show an improvement in outcomes with combination gemcitabine/erlotinib in metastatic pancreatic cancer. With the recent FDA approval of combination nab-paclitaxel/gemcitabine, the practical utility of erlotinib in pancreatic cancer is significantly decreased.

**Conclusions**

Presently, the utility of epidermal growth factor receptor (EGFR)-blocking agents is limited to a small number of tumor types. Predictive biomarkers, including EGFR mutation in non–small-cell lung cancer and Kirsten rat sarcoma (K-ras) mutations in colorectal cancer, have been developed to help identify the subgroup of patients who may derive benefit from these agents. EGFR expression has not been found to predict response with EGFR antagonists. Moreover, a predictive biomarker in one cancer type is not helpful in another cancer type, suggesting that different mechanisms may be involved. Rash severity has been correlated with the efficacy of anti-EGFR agents, but it alone cannot be used as criteria for baseline selection. Preemptive skin treatment with skin moisturizers, sunscreen, topical steroids, and doxycycline may reduce the severity of the rash without compromising efficacy.\textsuperscript{67}

Tumor cells eventually develop resistance to anti-EGFR agents by using alternative growth factor receptor pathways or by constitutively activating downstream intracellular signals.\textsuperscript{68} Novel therapeutic strategies are needed to overcome resistance to EGFR antagonists. One such strategy is the development of afatinib, which is active against T790 mutant tumor cells (acquired mutation), although at a lower potency. Novel biomarkers also are needed to predict the development of resistance to these agents in individual patients, thus offering personalized therapy.

**References**


