Special Report

EGFR Targeting of Solid Tumors

Caio M. Rocha-Lima, MD, Heloisa P. Soares, MD, Luis E. Raez, MD, and Rakesh Singal, MD

Background: Recent clinical trials suggest that epidermal growth factor receptor (EGFR)-targeted agents could benefit many patients with cancer.

Methods: We review the current status of several EGFR-targeted therapies in cancer patients and address the efficacy of these drugs as monotherapy or in combination with other drugs and/or treatments.

Results: Cetuximab is the most widely studied anti-EGFR monoclonal antibody. Other monoclonal antibody agents under investigation are panitumumab, matuzumab, MDX-447, nimutozumab, and mAb806. Extensive research has also evaluated the efficacy of EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib, EKB-569, lapatinib (GW572016), PKI-166, and canertinib (CI-1033). All of these agents have been studied for the treatment of colorectal, lung, breast, pancreatic, renal, head and neck, gynecologic, and prostate cancer. Currently, cetuximab and panitumumab are FDA approved for the treatment of metastatic colorectal cancer. Additionally, cetuximab is approved for head and neck cancer. Erlotinib is FDA approved for advanced/metastatic lung cancer. Erlotinib in combination with gemcitabine is approved for advanced/metastatic pancreatic cancer treatment.

Conclusions: EGFR-targeted agents have already shown utility in different scenarios. Researchers are continuously investigating additional cancer types and combined treatment modalities that could also benefit from the use of EGFR-targeted agents. Careful patient selection through the identification of specific biologic markers, such as gene expression, genomic polymorphism, and posttranslational modifications of EGFR downstream effectors, most likely will contribute to the successful use of these agents.

Introduction

Despite major advances in the management of cancer, most types of solid tumors remain resistant to conventional treatment modalities. In recent years there has been substantial interest in developing novel therapeutic agents that specifically target growth factor pathways that are dysregulated in tumor cells. Such targetted “biologic” agents might offer alternative treatment options for patients sensitive or refractory to standard chemotherapy. Also, with unique mechanisms of action and toxicity profiles that generally do not overlap, targeted agents and standard therapies can be used in combination to enhance overall treatment efficacy and prevent dose reductions.

In particular, agents targeting members of the human epidermal growth factor receptor family — EGFR 1 (also known as EGFR) and EGFR 2 — have shown encouraging therapeutic efficacy. The first to be approved by the US Food and Drug Administration (FDA) in 1998 was trastuzumab (Herceptin) for the treatment of HER-2 (ErbB-2)-positive breast cancer. Over the past few years, three EGFR (EGFR1/ErbB-1)-specific agents have also received regulatory approval: cetuximab (Erbitux) for metastatic colorectal cancer (mCRC) and squamous cell carcinoma of the head and
neck (SCCHN), erlotinib (Tarceva) for advanced or metastatic pancreatic cancer and non-small-cell lung cancer (NSCLC), and gefitinib (Iressa) for advanced or metastatic NSCLC. However, FDA approval for gefitinib was recently withdrawn after it failed to demonstrate a survival benefit either alone or with chemotherapy in three phase III trials.\(^1\)\(^2\)\(^3\)

EGFR is a rational target in solid tumors. Activation of the EGFR promotes processes responsible for tumor growth and progression, including proliferation and maturation, angiogenesis, invasion, metastasis, and inhibition of apoptosis (Figure). In addition, EGFR expression has been detected to varying degrees in a wide range of solid tumors (Table 1). Although the prognostic significance of EGFR expression remains unclear, as reports on this issue are contradictory, a retrospective review of EGFR studies reported that EGFR expression levels are highly predictive of clinical outcome for patients with head and neck, ovarian, cervical, bladder, and esophageal cancers. They are of moderate prognostic value for gastric, breast, endometrial, and colorectal tumors and of relatively low prognostic value for NSCLC.\(^4\) EGFR gene amplification or mutation and dysregulation of EGFR-mediated signaling pathways have also been detected in various malignancies (further discussed herein).

Recently completed and ongoing clinical trials suggest that EGFR-targeted agents have potential utility in multiple indications. Moreover, their efficacy may be enhanced by combination with other targeted agents such as bevacizumab, an antibody to vascular endothelial growth factor (VEGF), which is itself FDA approved in combination with chemotherapy for the treatment of mCRC and metastatic NSCLC.\(^5\) This review presents the current status of EGFR-targeted therapy in solid tumors.

**EGFR Inhibition**

The EGFR consists of an extracellular ligand-binding domain, a hydrophobic membrane-spanning region, and an intracellular tyrosine kinase domain. The most clini-
cally advanced EGFR inhibition strategies include monoclonal antibody-mediated blockade of the extracellular ligand-binding domain and small-molecule inhibition of the intracellular tyrosine kinase domain (Table 2).

**Monoclonal Antibodies**

Cetuximab (Erbitux) is the most extensively studied anti-EGFR monoclonal antibody. It is currently approved in several countries as monotherapy or in combination with irinotecan for the treatment of patients with irinotecan-refractory mCRC, as monotherapy for metastatic SCCHN, or in combination with radiation therapy for unresectable SCCHN.

Cetuximab is a chimeric monoclonal G1 (IgG1) antibody that binds to the EGFR with high affinity. The antibody blocks ligand binding and induces receptor internalization and degradation, resulting in downregulation of surface EGFR expression. In a dose-dependent manner, cetuximab inhibits the growth and proliferation of several tumor cell lines and xenograft tumors through putative mechanisms. These mechanisms include blocking the G1 phase of the cell cycle, promoting programmed cell death, or both, and inhibiting tumor angiogenesis. Cetuximab also has been shown to block the transport of EGFR into the nucleus, preventing activation of an important DNA-repair kinase, DNA-PK, implying that cetuximab could sensitize tumor cells to conventional DNA-damaging chemotherapies and radiation. As an IgG1 isoform of antibody, cetuximab also has the potential to mediate host immune responses such as antibody-dependent cell-mediated cytotoxicity (ADCC).

Other monoclonal antibodies currently undergoing evaluation in preclinical and clinical trials include panitumumab (ABX-EGF), matuzumab (EMD-72000), MDX-447, nimotuzumab (h-R3), and mAb806, an antibody directed against a mutant form of EGFR (EGFR vIII) that

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Percentage of Tumors Expressing EGFR</th>
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<tbody>
<tr>
<td>Head and neck</td>
<td>80 – 100</td>
</tr>
<tr>
<td>Renal</td>
<td>50 – 90</td>
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<tr>
<td>Lung</td>
<td>40 – 80</td>
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<tr>
<td>Breast</td>
<td>14 – 91</td>
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<tr>
<td>Colon</td>
<td>25 – 77</td>
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<td>Ovarian</td>
<td>35 – 70</td>
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<tr>
<td>Prostate</td>
<td>39 – 47</td>
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<tr>
<td>Glioma</td>
<td>40 – 63</td>
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<tr>
<td>Pancreas</td>
<td>30 – 50</td>
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<tr>
<td>Bladder</td>
<td>31 – 48</td>
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<thead>
<tr>
<th>Agent</th>
<th>Tumor Target</th>
<th>Status</th>
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<tbody>
<tr>
<td><strong>Monoclonal Antibodies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab (C225)</td>
<td>Colorectal, SCCHN, NSCLC, pancreatic, breast, cervical, endometrial, gastric, hepatocellular, ovarian, renal cell</td>
<td>Approved for colorectal and SCCHN; phase II/III for other indications</td>
</tr>
<tr>
<td>Panitumumab (ABX-EGF)</td>
<td>Colorectal, RCC, NSCLC</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Matuzumab (EMD-72000)</td>
<td>Head and neck, colorectal, gastroesophageal, ovarian, cervical</td>
<td>Phase I</td>
</tr>
<tr>
<td>Nimotuzumab (h-R3)</td>
<td>Glioma, NSCLC</td>
<td>Phase I</td>
</tr>
<tr>
<td>MDX-447</td>
<td>Head and neck</td>
<td>Phase I</td>
</tr>
<tr>
<td>mAb806</td>
<td>Glioma, epithelioid carcinoma</td>
<td>Preclinical</td>
</tr>
<tr>
<td><strong>Tyrosine Kinase Inhibitors</strong></td>
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<td>Gefitinib (ZD1839)</td>
<td>NSCLC, colorectal, head and neck, breast, prostate, bladder, esophageal</td>
<td>Approval for the use of gefitinib in previously treated NSCLC has been withdrawn after results of the ISEL trial; phase II/III for other indications</td>
</tr>
<tr>
<td>Erlotinib (OSI-774)</td>
<td>NSCLC, pancreatic, head and neck, breast, ovarian, prostate, colorectal, glioblastoma multiforme</td>
<td>Approved for NSCLC and pancreatic; phase II/III for other indications</td>
</tr>
<tr>
<td>Lapatinib (GW572016)</td>
<td>NSCLC, esophageal, breast, ovarian, head and neck, prostate, glioblastoma multiforme</td>
<td>Phase II/III</td>
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<tr>
<td>Canertinib (CI-1033)</td>
<td>Skin, squamous cell carcinoma, NSCLC</td>
<td>Phase I</td>
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<tr>
<td>EKB-569</td>
<td>Colorectal</td>
<td>Phase I</td>
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<tr>
<td>PKI-166</td>
<td>Kidney, prostate</td>
<td>Phase I</td>
</tr>
<tr>
<td>PD153035</td>
<td>Breast, glioma, head and neck</td>
<td>Preclinical</td>
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ISEL = Iressa (gefitinib) Survival Evaluation in Lung Cancer.
also recognizes overexpressed wild-type EGFR receptor.\textsuperscript{9,10} Of these, the most well studied is panitumumab, a fully human monoclonal IgG2 antibody that, like cetuximab, competitively inhibits EGFR ligand binding, promotes receptor internalization, and prevents tyrosine kinase phosphorylation. Unlike cetuximab, however, panitumumab does not induce receptor degradation upon internalization, suggesting that the EGFR may be recycled to the cell surface.\textsuperscript{11} As an IgG2 isoform of antibody, panitumumab is also unlikely to mediate ADCC responses.\textsuperscript{8}

**Tyrosine Kinase Inhibitors**

The two most clinically advanced EGFR tyrosine kinase inhibitors are erlotinib and gefitinib. Erlotinib (Tarceva) is indicated as monotherapy in treatment-refractory advanced or metastatic NSCLC and in combination with gemcitabine for the first-line treatment of advanced, unresectable, or metastatic pancreatic cancer.

Erlotinib and gefitinib both selectively and reversibly inhibit phosphorylation of the EGFR tyrosine kinase without inducing EGFR internalization or degradation. Inhibition of EGFR downstream signaling by erlotinib and gefitinib exerts antitumor activity through inhibition of proliferation and tumor angiogenesis and through induction of apoptosis.\textsuperscript{12}

Other tyrosine kinase inhibitors currently in clinical trials include EKB-569, lapatinib (GW572016), PKI-166, and canertinib (CI-1033).\textsuperscript{13} EKB-569 is an irreversible inhibitor of EGFR, and lapatinib and PKI-166 are reversible dual inhibitors of EGFR and HER-2 tyrosine kinases. Canertinib is an irreversible inhibitor of multiple EGFR family tyrosine kinases, in particular EGFR and HER-2.

**Current Status of EGFR-Targeted Agents in Solid Tumors**

**Colorectal Cancer**

Cetuximab was the first EGFR-targeted agent approved for the treatment of refractory mCRC. In the phase II European randomized BOND trial, single-agent cetuximab and cetuximab in combination with irinotecan were examined in patients with irinotecan-resistant tumors.\textsuperscript{14} Patients progressing on cetuximab alone (C) could cross over at the time of progression to cetuximab and irinotecan combination therapy (C + I).

Among the enrolled patients, 63\% had also undergone oxaliplatin therapy. The overall response (OR) rate for the combination of cetuximab and irinotecan was 22.9\% compared with 10.8\% for cetuximab monotherapy. The combination therapy resulted in a statistically significant increase in median time to disease progression (TTP) (4.1 months vs 1.5 months observed in the monotherapy group, \(P<.001\)); however, median survivals did not differ significantly between the two groups (8.6 months and 6.9 months, respectively). The response rates in patients with skin reactions from cetuximab treatment were higher than those in patients without skin reactions: 24.7\% for C + I and 12\% for C vs 16.7\% for C + I and 7.1\% for C, respectively.

In a subsequent phase II study evaluating the activity of cetuximab monotherapy in 346 patients with mCRC refractory to both irinotecan and oxaliplatin, cetuximab demonstrated a similar OR rate of 12\% and mean overall survival (OS) of 6.6 months.\textsuperscript{15} Cetuximab activity was consistent regardless of the number of prior lines of therapy or the sequence of prior agents.\textsuperscript{16}

The safety and efficacy of combined biologics (ie, cetuximab and bevacizumab), with or without irinotecan, were evaluated in the randomized BOND-2 study.\textsuperscript{17} No unexpected toxicities were observed during preliminary analysis of 65 patients. Patients receiving cetuximab, bevacizumab, and irinotecan (CBI) experienced a 38\% OR rate, and patients on cetuximab and bevacizumab (CB) experienced a 23\% OR rate. Median TTP in the CBI group was 8.5 months, faring better than the 6.9 months reported in the CB group (\(P<.01\)).\textsuperscript{17} The apparent increased efficacy of these treatment regimens, when retrospectively analyzed with those in the first BOND trial, brings hope for combining different biologic agents for patients with mCRC and other solid tumors.

The effectiveness of cetuximab for the first-line therapy of mCRC patients is being studied. An interim analysis of the international phase II ACROBAT trial indicated that cetuximab in combination with 5-fluorouracil (5-FU)/leucovorin/oxaliplatin (FOLFOX-4) resulted in a promising 72\% OR rate (n = 62) as first-line therapy in patients with mCRC.\textsuperscript{18} Additionally 23\% of patients had stable disease (SD). In another phase II study of first-line use of cetuximab, cetuximab with 5-FU/leucovorin/irinotecan (FOLFIRI) resulted in a 46\% partial response (PR) rate (n = 23) and a 10.9-month mean TTP.\textsuperscript{19} Phase III trials studying the addition of cetuximab to standard chemotherapy in mCRC and adjuvant therapy are ongoing: cetuximab/FOLFIRI vs FOLFIRI alone as first-line therapy for mCRC (CRYSTAL), cetuximab/FOLFOX vs FOLFOX alone as adjuvant therapy following curative resectioning of stage III colon cancer (NCCTG-N0147), and cetuximab/irinotecan vs irinotecan alone in second-line treatment of mCRC (EPIC).

Other EGFR-targeted monoclonal antibodies for mCRC include panitumumab. A phase II multicenter study of panitumumab monotherapy in refractory disease has indicated a 10.1\% PR rate (n = 148) with a low incidence of infusion reactions and otherwise mild adverse effects.\textsuperscript{20} In refractory mCRC, panitu-
mumab as a single agent reduced the risk of tumor progression by 46% compared with best supportive care. An ongoing phase III study (PACCE) is evaluating the combination of oxaliplatin-based chemothera-

py and bevacizumab with or without panitumumab as first-line therapy in mCRC.

The combination of gefitinib (500 mg/day) and FOLFOX-4 (IFOX) produced a 32% PR rate (n = 27) in previously treated mCRC patients. Results from a par-

allel study of the IFOX regimen as first-line treatment for mCRC revealed an impressive OR rate of 78%. The drawback of both studies was significant toxicity, with approximately half of the enrolled patients experienci-
ging grade 3 or 4 diarrhea and a similar proportion of patients experiencing grade 3 or 4 neutropenia.

**Lung Cancer**

Erlotinib is currently approved for use as monotherapy in treatment-refractory, advanced NSCLC. The large, randomized phase III BR.21 trial, which investigated erlotinib (150 mg/day) as second- or third-line therapy in 731 patients with metastatic NSCLC (mNSCLC), demonstrated a significant OS benefit from erlotinib monotherapy (6.7 months vs 4.7 months with placebo; P= .001) and a 10% improvement in the 1-year survival rate. This was the first randomized trial to confirm that an EGFR inhibitor can prolong survival in advanced NSCLC after first- or second-line chemotherapy.

Initial accelerated approval for gefitinib was based on early results in tumor response rates in the phase II IDEAL-1 and -2 trials, which demonstrated an 8.8% to 19% response rate in patients treated with doses of 250 or 500 mg/day. Gefitinib approval was recently withdrawn, however, when final data from these trials and from a subsequent phase III trial failed to demonstrate a significant survival benefit from gefitinib monotherapy compared with placebo. The primary endpoint of Study 709, Iressa (gefitinib) Survival Evaluation in Lung Cancer (ISEL) with 1,692 patients, showed that gefitinib failed to significantly prolong survival in comparison to placebo in the overall population (hazard ratio = 0.89, P=.11, median 5.6 vs 5.1 months), or in patients with adenocarcinoma (hazard ratio = 0.83, P=.07, median 6.3 vs 5.4 months). There was a statistically significant improvement in tumor shrinkage (objective response rate), which did not translate into a statistically significant survival benefit. Subsets of the patient population in these studies, including Asians and never-smokers, did experience significant clinical improvement and provided a basis for further studies. Gefitinib is currently indicated only for NSCLC patients who have already received benefit from gefitinib.

Neither erlotinib nor gefitinib has demonstrated clinical benefit when added to standard chemotherapy as first-line treatment for advanced NSCLC. This disap-

pointing finding suggests that these agents do not have utility in this setting. The INTACT phase III trials evaluated the safety and efficacy of adding gefitinib to gemcitabine/cisplatin (INTACT-1) or gefitinib to paclitaxel/carboplatin (INTACT-2) in the treatment of chemothera-

py-naive patients with advanced or metastatic NSCLC. No clinical benefit was observed relative to chemotherapy alone. Similarly, two phase III trials of erlotinib (150 mg/day) combined with carboplatin/paclitaxel (TRIBUTE) or with cisplatin/gemcitabine (TALENT) in first-line treatment of mNSCLC both failed to meet their primary endpoint of improving OS.

A phase I/II study of erlotinib 150 mg/day com-

bined with bevacizumab 15 mg/kg administered intra-

venously in stage IIIb/IV recurrent NSCLC revealed no pharmacokinetic interaction between the two agents and showed 20% PR rate (n = 40), 65% SD rate, 12.6-

month median survival, and 6.2-month progression-free survival (PFS).

The first randomized phase II study combining erlotinib with docetaxel, pemetrexed, or bevacizumab was presented at ASCO 2006. The results are prelimi-

nary from a phase II trial, but they showed the possi-

bility to increase OR rate with the combination of these agents with erlotinib.

Current study of tyrosine kinase inhibitors is focusing on stratifying populations that will respond to therapy. The discovery of gene mutations in the tyro-
sine kinase domain and the discovery that gene ampli-

fication might be strongly associated to response to these agents may help in identifying patients who will benefit the most from these drugs. Cetuximab is in late-stage clinical testing in advanced NSCLC. Phase II studies of cetuximab combined with cisplatin/ vinorelbine (n = 81) showed a 31.7% response rate compared with a 20% response rate with chemotherapy alone, and this combination is being investigated as first-line therapy for NSCLC in the ongoing phase III FLEX trial. Cetuximab has also shown encouraging results in phase I/II studies in combination with docetaxel, paclitaxel/carboplatin, and gemcitabine/carboplatin and is being investigated in phase II and III studies in combination with these chemotherapy regimens. A randomized phase III trial comparing docetaxel or pemetrexed with or without cetuximab in patients with recurrent or progressive NSCLC after platinum-based therapy is in progress. Single-agent cetuximab treatment in recurrent or metastatic NSCLC following one or more prior chemotherapy regimens resulted in only 4.5% PR rate (n = 66) and 30% SD rate in a phase II study. Early results of a phase II trial evaluating weekly panitumumab in combination with paclitaxel/carboplatin in 19 patients with advanced NSCLC demonstrated a 5% confirmed complete response rate (at 1.0 mg/kg) and 21% PR rate (2 at 2.0 mg/kg and 2 at 2.5 mg/kg).
Pancreatic Cancer

A phase III study for first-line treatment of advanced pancreatic cancer showed that the addition of erlotinib to gemcitabine significantly improved OS compared with gemcitabine alone; the median survival was 6.24 vs 5.91 months, the 1-year survival rate was 23% vs 17% \((P=0.023)\), and the PFS hazard ratio was 0.77 \((P=0.004)\). These results led to the recent approval of erlotinib in combination with gemcitabine for this patient population.

EGFR inhibition in pancreatic cancer has been rewarding. The addition of cetuximab to gemcitabine was evaluated in a multicenter phase II trial for the treatment of advanced pancreatic cancer and gave promising results: 12.2% PR rate and 63.4% SD rate (7.1 months median OS, 3.8 months median TTP, 12% 1-year PFS rate, and 31.7% OS rate) in 41 evaluable patients.\(^6\) This combination, compared with single-agent gemcitabine, is currently being investigated in a large Southwest Oncology Group phase III trial as first-line therapy for pancreatic cancer.

An ongoing randomized phase II study evaluating bevacizumab/gemcitabine combined with either cetuximab or erlotinib may provide additional “head to head” information about the two classes of EGFR inhibitors.

Head and Neck Cancer

Cetuximab is the first targeted agent to demonstrate a survival advantage in combination with radiation therapy in SCCHN. In a phase III trial involving 424 patients with locoregionally advanced SCCHN, the addition of cetuximab to high-dose radiation resulted in a median survival of 49 months compared with 29 months with radiation alone and a 26% reduction in the risk of mortality \((P=0.03)\).\(^5\) Cetuximab did not exacerbate grade 3 or 4 toxicities associated with radiation therapy, although expected additional adverse effects (ie, acniform rash and a low incidence of infusion reactions) occurred. Based on this study, the FDA recently approved cetuximab use in combination with radiation therapy for first-line treatment of locally or regionally advanced SCCHN and as a single-agent therapy for treatment of recurrent or metastatic SCCHN refractory to platinum-based chemotherapy.

In a phase III trial, cetuximab combined with cisplatin achieved a 26% OR rate compared with 10% with cisplatin alone \((P=0.03)\), but it had no significant effect on PFS and OS in 112 patients with recurrent/metastatic SCCHN.\(^8\) Ongoing phase II studies are evaluating cetuximab as neoadjuvant induction therapy with paclitaxel, carboplatin, and radiotherapy in patients with stage III/IV SCCHN and cetuximab in combination with cisplatin and radiation for patients with locally advanced, inoperable stage IV SCCHN or undifferentiated carcinoma of the head and neck.

In a phase II trial, gefitinib monotherapy (500 mg/day) for recurrent or metastatic SCCHN resulted in a 10.6% OR rate, 53% disease control, and a median survival time of 8 months;\(^9\) however, a 250-mg/day dose in another phase II trial resulted in only one PR (1.4%).\(^4\) In a multicenter phase II study, erlotinib (150 mg/day) showed minimal efficacy (4.3% OR rate) in 115 patients with heavily pretreated recurrent or metastatic SCCHN.\(^1\)

Renal Cell Carcinoma

Panitumumab (ABX-EGF), a fully human monoclonal antibody targeting the EGFR, was studied in previously treated patients with metastatic renal cell carcinoma (RCC) at doses of 1.0, 1.5, 2.0, or 2.5 mg/kg weekly with no loading dose. Of 88 patients, major responses were seen in 3 patients (3.4%), minor responses in 2 patients (2.3%), and SD in 44 patients (50%) at their first 8-week assessment. The median PFS was 100 days (95% CI, 58 to 140 days).\(^12\)

Gefitinib monotherapy (500 mg/day) has been evaluated in two phase II studies in advanced RCC. The first study enrolled 21 patients. The best response was SD in 8 patients (38%). Median PFS and OS were 2.7 months and 8.3 months, respectively.\(^3\) In another study with 28 patients, no objective responses were seen, but 14 patients (53.8%) had SD. Median TTP was 110 days and median OS was 303 days.\(^14\)

Erlotinib (150 mg/day) combined with bevacizumab (10 mg/kg administered intravenously once every 2 weeks) in a phase II trial demonstrated a 25% OR rate and a further 61% SD rate in 59 assessable patients with mRCC after 8 weeks of treatment. The median and 1-year PFS were 11 months and 43%, respectively. The median survival had not been reached at the time of reporting (median follow-up of 15 months), and the survival rate at 18 months was 60%.\(^4\) Preliminary results of a phase I/II study also indicate activity of erlotinib/bevacizumab combined with imatinib, a platelet-derived growth factor (PDGF) receptor antagonist, in RCC with 9% PR rate and 61% minor response or SD rate.\(^4\) These findings suggest that EGFR-targeted agents might be most useful in mRCC as part of combination regimens targeting multiple tumor-related pathways.

Gynecologic Cancers

Several phase II clinical trials of EGFR inhibitors have been conducted in patients with gynecologic malignancies. To date, the most promising therapies include gefitinib or cetuximab combined with standard chemotherapy in ovarian cancer. In the treatment of patients with recurrent or refractory ovarian cancer, gefitinib combined with paclitaxel/carboplatin and gefitinib combined with vinorelbine/oxaliplatin achieved OR rates of 71% and 90%, respectively, in platinum-sensitive patients and 25% and 24%, respectively, in platinum-refractory patients.\(^47,48\) Preliminary data from a study examining cetuximab combined with paclitaxel/carboplatin in first-line therapy of advanced ovarian,
controlled phase II trials.\textsuperscript{56} Phase II trials of erlotinib in has shown little activity as monotherapy in randomized, EGFR-targeted agents in this disease. However, gefitinib response was expected to be proportional to the level of tumors that expressed the EGFR target, and tumor effectiveness was anticipated only in patients with

When EGFR-targeted agents first entered the clinic, their Respond to EGFR-Targeted Therapy

Preselection of Patients Most Likely to Respond to EGFR-Targeted Therapy

Breast Cancer
The clinical success of trastuzumab in HER-2-positive advanced or metastatic breast cancer has led to speculation that further improvements might be gained from EGFR-targeted agents in breast cancer. As first-line therapies in advanced or metastatic breast cancer, lapatinib monotherapy (1,000 to 1,500 mg/day) and gefitinib in combination with docetaxel resulted in 58% and 38% OR rates, respectively; these responses are comparable to those achieved by existing therapies.\textsuperscript{50,51} Neither gefitinib monotherapy (500 mg/day) nor gefitinib or erlotinib (150 mg/day) in combination with chemotherapy had significant activity in advanced or metastatic breast cancer.\textsuperscript{52-54} Current studies of EGFR-targeted agents in breast cancer are focusing on their utility in combination with hormone antagonists and in specific population subgroups (eg, patients who are estrogen receptor-positive with tamoxifen-resistant disease).

Prostate Cancer
Androgen-dependent prostate cancer is currently treated medically with antiandrogens. Although chemotherapeutic agents such as docetaxel have been successful in prolonging survival in hormone-refractory prostate cancer, there is room for improvement in androgen-independent disease. Immunohistochemistry-detectable EGFR expression has been shown to increase during prostate cancer progression to advanced, androgen-independent stages,\textsuperscript{55} providing a rationale for investigating EGFR-targeted agents in this disease. However, gefitinib has shown little activity as monotherapy in randomized, controlled phase II trials.\textsuperscript{56} Phase II trials of erlotinib in prostate cancer are ongoing.

EGFR gene amplification has been associated with response to cetuximab or panitumumab in mCRC patients.\textsuperscript{68} Increased EGFR gene copy number was also associated with improved survival in patients with NSCLC and advanced bronchioalveolar carcinoma treated with gefitinib monotherapy\textsuperscript{69,70}; however, such an association did not exist for a combination of gefitinib and chemotherapy in NSCLC.\textsuperscript{65} Amplification of the HER-2 gene was also associated with gefitinib activity in NSCLC.\textsuperscript{71} The BR.21 study also failed to demonstrate any association between EGFR gene copy number and survival in patients with NSCLC treated with single-agent erlotinib.\textsuperscript{65} The true correlation between EGFR/HER-2 gene amplification and sensitivity to different EGFR-targeted therapies remains an important focus of clinical investigations.

EGFR expression. Therefore, cetuximab mCRC trials were conducted in patients whose tumors tested positive for EGFR expression by immunohistochemistry. However, studies failed to demonstrate a consistent relationship between pretreatment-measured tumor EGFR expression and response to cetuximab therapy in patients with mCRC.\textsuperscript{14,15,57} Moreover, responses to cetuximab have been documented in patients with tumors identified as EGFR negative.\textsuperscript{58,59} As a result of these findings, selection of patients for cetuximab therapy using EGFR-expression criteria is discouraged by the National Comprehensive Cancer Network,\textsuperscript{60} although current FDA-approved indications for cetuximab, based on criteria established for the initial clinical trials, specify positive EGFR expression as a parameter for patient selection.

Similarly, no relationship between EGFR expression and tumor response to gefitinib could be identified in the IDEAL NSCLC trials.\textsuperscript{61,62} Reassessment of the role of EGFR expression in predicting tumor response and the search for more reliable prognostic markers for EGFR-targeted agents are strong objectives in the field.

Activating EGFR mutations in the tyrosine kinase inhibitor binding domain have been correlated with clinical response to gefitinib and erlotinib monotherapy in NSCLC. Recent analyses reveal objective response rates to gefitinib in patients harboring EGFR mutations to be between 46% and 65%.\textsuperscript{63,64} In erlotinib-treated NSCLC patients in the BR.21 trial,\textsuperscript{65} the presence of EGFR mutations correlated with response rates but not improved survival. Recent reports describe the EGFR mutation, T790M, associated with gefitinib and erlotinib resistance in NSCLC.\textsuperscript{66} Activating mutations in the downstream GTPase, KRas, have also been associated with lack of sensitivity to erlotinib in NSCLC patients.\textsuperscript{67} The clinical significance of activating mutations will depend on their prevalence in cancer patients because somatic mutations in the EGFR appear to be rare in certain cancer types. Such mutations seem to be of little relevance to the efficacy of anti-EGFR monoclonal antibodies.

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Downstream effectors of EGFR activation may act as more accurate biologic markers of tumor EGFR “status” and of potential responsiveness to EGFR-targeted agents. In a phase II trial of gefitinib in patients with advanced breast cancer, gefitinib effectively inhibited phosphorylation of MEK in skin and tumor cells (indicating effective EGFR inhibition) but altered only p27 and Ki67 in skin and not in tumors. These findings provide an explanation for the lack of efficacy of gefitinib in this study. In NSCLC patients who were treated with gefitinib, phosphorylated Akt status was significantly associated with better response rate, improved disease control rate, and longer TTP, but not improved survival. In another trial, low phosphorylated MAPK predicted increased survival with gefitinib therapy in patients with bronchioloalveolar carcinoma. Increased understanding of downstream signaling pathways of EGFR activation, combined with new technology such as gene and protein arrays to screen multiple markers in single patients, should guide more accurate preselection of patients who are most likely to respond to EGFR-targeted agents.

Conclusions

Biologic targeted therapies, such as EGFR-targeted agents, are being used increasingly for the treatment of patients with solid tumors. Also, these agents are currently being explored as monotherapy or in combination with radiation, chemotherapy, or other biologically targeted agents for the treatment of aggressive tumors that frequently resist conventional cytotoxic regimens. The value of targeted agents in combination with cytotoxic therapies lies in the potential for improved (additive or synergistic) responses with minimal increases in toxicity, new ability to reduce doses of cytotoxic agents, and overall improved quality of life.

The first cancers to be effectively treated with EGFR-targeted therapies were mCRC and advanced or metastatic NSCLC, leading to approval of cetuximab for mCRC and erlotinib for NSCLC. Most recently, cetuximab was approved as monotherapy in SCCHN and in combination with radiotherapy for both loco-regional modifications of EGFR downstream effectors.

References


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