Abstract

Molecular targeting strategies for cancer therapy are distinct from conventional chemotherapy and radiotherapy in their potential to provide increased tumor specificity. One particular molecular target of high promise in oncology is the epidermal growth factor receptor (EGFR). The EGFR is overexpressed, dysregulated or mutated in many epithelial malignancies, and EGFR activation appears important in tumor growth and progression. Advances in signal transduction biology continue to sharpen our understanding regarding specific contributions of EGFR signaling networks to cancer behavior. Two predominant classes of EGFR inhibitors have been developed including monoclonal antibodies (mAbs) that target the extracellular domain of EGFR, such as cetuximab (Erbitux), and small molecule tyrosine kinase inhibitors (TKIs) that target the receptor catalytic domain of EGFR, such as gefitinib (Iressa) and erlotinib (Tarceva).

Mechanisms of action for EGFR inhibitors have been investigated in preclinical model systems. Safety, activity, pharmacokinetics and pharmacodynamics have been assessed in clinical trials. The anti-EGFR mAbs and TKIs have partially overlapping toxicity profiles, but distinct routes of administration, serum half-lives and therefore dosing schedules. Both classes of agents show clear antitumor activity, and cetuximab and gefitinib have been recently FDA approved for colorectal and lung cancer indications respectively. However, the absence of survival benefit for EGFR TKIs in combination with chemotherapy in large-scale phase III lung cancer trials in 2003 underscores a major challenge in anti-EGFR oncology therapeutics; namely to identify those tumors and patients that will respond predictably to EGFR inhibitor approaches. Newly identified mutations in the EGFR catalytic domain that appear to confer sensitivity to EGFR TKIs promise to open new doors of investigation regarding response prediction. Advances will also require enhanced molecular understanding of the overall EGFR signaling network, and improved methods to gauge the dependence of individual tumors on EGFR signaling pathways for growth advantage. Results from newly reported phase III trials in 2004 now confirm a survival advantage for the use of EGFR inhibitors in combination with high-dose radiation in head and neck cancer, and in refractory lung cancer respectively. It appears likely that EGFR inhibitors (and other rationally designed molecular growth inhibitors) will play a meaningful role in cancer therapy in the years to come.

Introduction

Considerable progress has been made over the last several decades in understanding specific cellular, molecular and genetic mechanisms that contribute to cancer growth and progression. This improved mechanistic understanding of cancer has fostered the design, development, and clinical evaluation of more tumor-specific anticancer treatment approaches.

This review focuses on one particularly promising anticancer treatment strategy, namely that of epidermal growth factor receptor (EGFR) signaling inhibition. The most clinically advanced approach to EGFR inhibition includes the use of monoclonal antibodies (mAbs) directed against the EGFR extracellular domain, and the use of small molecule tyrosine kinase inhibitors (TKIs) directed against the tyrosine kinase domain. The mAbs
function at the extracellular ligand-binding site of the receptor, whereas the small molecule TKIs function at the intracellular tyrosine kinase domain of the EGFR.

**EGFR structure and function**

Growth factors and their transmembrane receptor kinases play important roles in cell proliferation, survival, adhesion, migration and differentiation (Yarden 2001). The EGFR family consists of four transmembrane receptors, including EGFR (HER1/erbB-1), HER2 (erbB-2/neu), HER3 (erbB-3) and HER4 (erbB-4) (Yarden 2001). The EGFR (HER1/erbB-1) is a 170 kDa protein comprising three major functional domains: an extracellular ligand-binding domain, a hydrophobic transmembrane domain and a cytoplasmic tyrosine kinase domain, as illustrated in Fig. 1.

Seven genetically distinct ligands — EGF, transforming growth factor-α (TGF-α), heparin-binding EGF, amphiregulin, betacellulin, epirotin and neuregulin G2β — have been shown to be capable of binding with EGFR (Watanabe et al. 1994, Toyoda et al. 1997, Wells 1999). Cognate ligand binding triggers erbB receptor aggregation, the formation of receptor homodimers and/or heterodimers, and internalization (Yarden 2001, Wiley 2003). Dimer formation leads to activation of the intrinsic receptor tyrosine kinase domain. Protein phosphorylation and dephosphorylation, catalyzed by protein kinases (such as tyrosine kinase) and protein phosphatases respectively, represent fundamental biochemical events for subsequent intracellular signal transduction (Qu 2002). Autophosphorylation of tyrosine residues within the C-terminal tail of EGFR in the cytoplasm (Cohen 2003) following EGFR tyrosine kinase activation initiates a cascade of intracellular signaling pathways (Carpenter & Cohen 1990). The receptor tyrosine kinase signal can be terminated by endocytosis of the phosphorylated receptor–ligand complex (Yarden 2001).

The EGFR downstream intracellular signal transduction pathways include components of the Ras/mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase, signal transducer and activator of transcription, downstream protein kinase C and phospholipase D pathways (Wells 1999, Carpenter 2000, Grant et al. 2002). Some of these pathways serve to attenuate receptor signaling (Wells 1999). Figure 2 is a simplified schematic illustrating the interaction of the EGFR system and the Ras/MAPK cascade, one of the major signaling routes (Alroy & Yarden 1997), and its downstream effects on the cell-cycle machinery. Yarden & Sliwkowski (2001) pro-
vide a comprehensive description of ErbB signaling pathways. The integrated biological responses to EGFR signaling are pleiotropic. They include mitogenesis, apoptosis, altered cellular motility, protein secretion and differentiation or dedifferentiation (Wells 1999).

EGFR — significance in oncology

Activation of the EGFR stimulates tumor growth and progression, including the promotion of proliferation, angiogenesis, invasion, metastasis and inhibition of apoptosis (Salomon et al. 1995, Wells 1999, Woodburn 1999). EGFR is normally widely expressed by many cell types, including those of epithelial and mesenchymal lineages (Wells 1999). However, there is variability regarding the reported incidence of overexpression or dysregulation of EGFR in human malignancies (Nicholson et al. 2001, Arteaga 2002). For example, some reports describe EGFR expression as being dysregulated in at least 50% of human epithelial tumors (Aaronson 1991, Earp et al. 2003, Grunwald & Hidalgo 2003a), while more conservative estimates suggest that one-third of epithelial malignancies express high levels of EGFR (Mendelsohn 2001). This variability may be partially attributable to a lack of standardization in quantitation methodology, using either simple immunohistochemistry or more sophisticated fluorescence in situ hybridization techniques. Overall, it does appear that many of our most common human epithelial cancers richly express the EGFR.

In head and neck cancer, the vast majority of tumors are strongly EGFR-positive (Mendelsohn 2001). Studies have also reported EGFR overexpression in the following cancers: bladder, brain, breast, cervical, uterine, colon, esophageal, glioma, non-small-cell lung cancer (NSCLC), ovarian, pancreatic and renal cell (Table 1) (Nicholson et al. 2001, Herbst 2002, Mendelsohn & Baselga 2003). A review of 200 studies (involving >20,000 patients) was undertaken to determine the prognostic value of increased EGFR expression for reduced recurrence-free or overall survival rates (Nicholson et al. 2001). Of the ten cancer types for which there were adequate data for analysis, the...
prognostic value was strong (70%) for head and neck, ovarian, cervical, bladder and esophageal cancers; moderate (52%) for gastric, breast, endometrial and colorectal tumors; and weak (30%) for NSCLC. Nonetheless, we now know that some patients with high levels of EGFR expression are refractory to EGFR inhibitor treatment, suggesting that mere expression of EGFR is not a robust predictor of response to therapy. Preclinical studies on 60 cell lines of the United States National Cancer Institute Anticancer Drug Screen were performed with a panel of 11 selective erbB inhibitors. Cell lines expressing high levels of EGFR could be divided into two groups, depending on their sensitivity or insensitivity to EGFR inhibitors (Bishop et al. 2002). The level of EGFR expression for the specific tumor appeared to be less important than the degree of activation of EGFR in predicting the response to targeted therapy. Factors affecting activation status include receptor mutation, heterodimerization and increased expression of ligands (Arteaga 2002). Signaling complexity due to interactions among four receptors and ten ligands makes it difficult to definitively measure signaling output for individual human tumors (Earp et al. 2003). The lack of a clear relationship between the level of EGFR expression and the degree of EGFR activation across tumor types complicates simple prediction of clinical effectiveness of targeted therapeutics (Arteaga & Baselga 2003).

Inhibition of EGFR in cancer

Mechanisms of action of EGFR inhibitors

mAbs directed against EGFR have the following mechanisms of action: (i) extracellular binding; (ii) internalization of receptor-antibody complexes; (iii) inhibition of EGFR signaling pathways; and (iv) potential stimulation of an immunological response.

TKIs directed against EGFR have the following mechanisms of action: (i) intracellular binding; (ii) prevention of tyrosine kinase activation; and (iii) inhibition of EGFR signaling pathways.

The respective sites of action of mAbs and TKIs are illustrated in Fig. 2.

mAb EGFR inhibitors

Several mAbs directed against EGFR are in various stages of clinical development. These antibodies are listed in Table 2.

Cetuximab

The most extensively studied of the anti-EGFR mAbs is cetuximab (Erbtitux; ImClone Systems), formerly known as IMC-225 or C225, a chimeric mAb designed to specifically inhibit EGFR (Ennis et al. 1991). Cetuximab has been recently approved (February 2004) by the US Food and Drug Administration and the Swiss Medicines Control Agency for the treatment of colorectal cancer that is unresponsive to irinotecan (Camptosar).

The chimeric antibody was developed by combining the variable regions of the precursor mouse antibody (mAb 225) with human immunoglobulin G1 constant regions to reduce the possibility of an antimouse immunological reaction in patients (Herbst & Shin 2002). Cetuximab is highly specific for EGFR, competing for natural ligand-binding sites and causing receptor internalization and downregulation (Kim et al. 2001). It inhibits the proliferation of a range of human tumor cell lines expressing high levels of EGFR.

Table 1 Percentage of tumors overexpressing EGFR, by tumor type

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Percentage of tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>31–48</td>
</tr>
<tr>
<td>Breast</td>
<td>14–91</td>
</tr>
<tr>
<td>Cervix/uterus</td>
<td>90</td>
</tr>
<tr>
<td>Colon</td>
<td>25–77</td>
</tr>
<tr>
<td>Esophagael</td>
<td>43–89</td>
</tr>
<tr>
<td>Gastric</td>
<td>4–33</td>
</tr>
<tr>
<td>Glioma</td>
<td>40–63</td>
</tr>
<tr>
<td>Head and neck</td>
<td>80–100</td>
</tr>
<tr>
<td>Ovarian</td>
<td>35–70</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>30–89</td>
</tr>
<tr>
<td>Prostate</td>
<td>40–80</td>
</tr>
<tr>
<td>Renal cell</td>
<td>50–90</td>
</tr>
<tr>
<td>Non-small-cell lung</td>
<td>40–80</td>
</tr>
</tbody>
</table>

prediction of clinical effectiveness of targeted therapeutics (Arteaga & Baselga 2003).

Table 2 EGFR monoclonal antibodies in clinical trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
<th>Generic/trade name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMC-C225</td>
<td>Chimeric IgG1</td>
<td>*Cetuximab/Erbtitux</td>
<td>ImClone/BMS/Merck KGaA</td>
</tr>
<tr>
<td>ABX-EGF</td>
<td>Fully human IgG2</td>
<td>panitumumab</td>
<td>Abgenix/Amgem</td>
</tr>
<tr>
<td>EMD 72000</td>
<td>Humanized IgG1</td>
<td>—</td>
<td>EMD Pharms/Merck KGaA</td>
</tr>
<tr>
<td>MDX-447</td>
<td>Humanized, bispecific: EGFR/FcR1</td>
<td>HuMab-Mouse</td>
<td>Medarex/Merck KGaA</td>
</tr>
<tr>
<td>h-R3</td>
<td>Humanized</td>
<td>TheraCIM</td>
<td>YM Biosciences/CIM</td>
</tr>
<tr>
<td>Mab 806</td>
<td>Anti-EGFR VIII</td>
<td>—</td>
<td>Ludwig Institute</td>
</tr>
</tbody>
</table>

*Approved.

The growth inhibitory impact of cetuximab in tumor xenograft models is often more pronounced than that observed in cell culture, suggesting that additional anticancer mechanisms are involved. One such mechanism involves anti-angiogenesis (Huang & Harari 1999, Mendelsohn 2001). Cetuximab inhibits vascular endothelial growth factor (VEGF) production in epidermoid carcinoma cells, resulting in a reduction in the number of tumor blood vessels (Viloria-Petit et al. 1997); down-regulation of VEGF, interleukin (IL)-8, and basic fibroblast growth factor (bFGF) expression in tumor xenografts; and inhibition of tumor blood vessels, with inhibition of tumor growth (Perrotte et al. 1999). In addition, cetuximab treatment significantly inhibits tumor growth and metastasis in mice bearing either 253J B-V tumors (Perrotte et al. 1999) or human prostate tumors (Karashima et al. 2002), and modestly inhibits spontaneous metastasis in a severe combined immunodeficiency mouse xenograft model of metastatic melanoma, an effect that may reflect antibody-dependent cellular cytotoxicity (Naramura et al. 1993, Mendelsohn 2001).

**ABX-EGF**

Other anti-EGFR mAbs in clinical development include the fully humanized ABX-EGF (Abgenix) selected from a panel of human IgG2 anti-EGFR mAbs generated by immunizing the XenoMouse IgG2 strain with cells of the human cervical epidermal cancer cell line A431, which express more than 10^6 EGFR molecules per cell (Davis et al. 1999, Yang et al. 1999, 2001). In vitro, AGX-EGF blocks the binding of both EGF and TGF-α to the receptor, inhibits EGFR-activated EGFR tyrosine phosphorylation and inhibits tumor cell activation and proliferation (Yang et al. 2001, Lynch & Yang 2002). Like cetuximab, ABX-EGF causes EGFR internalization in tumor cells and blocks activation of the EGFR tyrosine kinase.

In vivo experiments with human tumor xenografts in nude mice show that antitumor activity mediated by ABX-EGF correlates with the levels of EGFR expression on the human tumors tested. ABX-EGF blocks formation of human epidermoid carcinoma A431 xenografts in athymic mice, mediates therapeutic elimination of established tumors, and acts cooperatively with chemotherapeutic agents to cause tumor regression (Lynch & Yang 2002). Recently, in vitro and in vivo efficacy has been shown in studies of prostate cancer (Wang et al. 2003) and renal cell carcinoma (Wang et al. 2003) that were performed to support clinical trials for these indications. In the prostate tumor study, there was evidence of an anti-angiogenic effect (Wang et al. 2003).

**Other antibodies**

The humanized antibodies MDX-447 (Medarex), with dual activity against EGFR and the Fc receptor, and EMD 72000 (EMD Pharmaceuticals) are additional promising agents currently being evaluated in clinical trials for several tumors including head and neck cancer and ovarian cancer respectively. Unique antibodies raised against mutant forms of the EGFR (i.e. EGFRvIII) are also under development (Mishima et al. 2001) with growth suppression of intracranial xenografted glioblastomas overexpressing mutant EGFRs by systemic administration of mAb 806, a novel mAb directed to the receptor (Mishima et al. 2001). In this review, discussion is focused on the EGFR-specific mAbs cetuximab and ABX-EGF since they are the most advanced of their class.

**TKIs**

The TKIs are synthetic, mainly quinazoline-derived, low molecular weight molecules that interact with the intracellular tyrosine kinase domain of several receptors, including EGFR, and inhibit ligand-induced receptor phosphorylation by competing for the intracellular Mg-ATP-binding site (Ciardiello 2000). Over the past 20 years, several hundred TKIs have been developed (Ciardiello 2000). TKIs that target the EGFR and are sufficiently advanced in clinical development are shown in Table 3.

**Gefitinib**

Gefitinib (Iressa; AstraZeneca), formerly known as ZD1839, has received approval in 18 countries (to date) including the United States, Canada, Japan, Australia, and other countries in the Far East and the Americas, as a single agent for the treatment of refractive NSCLC. Gefitinib is an orally active, low molecular weight, synthetic anilinoquinazoline that inhibits several receptor tyrosine kinases, particularly EGFR (Ciardiello et al. 2000, Arteaga & Johnson 2001, AstraZeneca Pharmaceuticals LP 2003). Gefitinib inhibits the kinase activity of isolated EGFR with an IC_{50} in the nanomolar range (Woodburn et al. 2000). However, higher concentrations may be required to block EGFR activity in vivo, due to the high intracellular concentration of ATP (Arteaga & Johnson 2001). At concentrations more than 100-fold greater than those required to inhibit EGFR, gefitinib inhibits other tyrosine kinase receptors, including HER2 (Woodburn et al. 2000, Arteaga & Johnson 2001, Moulder et al. 2001). This additional receptor activity
may have clinical significance, and clinical studies in this regard are in progress.

Gefitinib demonstrates antiproliferative activity in tumor cell cultures and in human tumor xenografts, both as a single agent and in combination with cytotoxic chemotherapy or radiotherapy. With co-administration, gefitinib shows additive or even synergistic effects (Sirotnak et al. 2000, Sirotnak 2003). The additive or synergistic effects of gefitinib achieved in combination therapy did not necessarily require high levels of EGFR expression in the tumor models tested. These preclinical findings influenced subsequent clinical trial strategies where high level of EGFR expression by the tumor was not a criterion for study entry (see INTACT trials, below).

Preclinical studies indicate that gefitinib affects many of the same intracellular signaling pathways inhibited by anti-EGFR mAb therapy. Gefitinib inhibits the growth of a range of human cancer cells in vitro and in vivo, and there is evidence that the inhibitor acts by inducing cell-cycle arrest and/or apoptosis (Ciardiello et al. 2000, Woodburn et al. 2000, Albanell et al. 2001, Magne et al. 2002, Di Gennaro et al. 2003). As with the EGFR-specific mAbs, the TKIs appear to act by several antitumor mechanisms. Gefitinib appears to indirectly inhibit angiogenesis since treatment is associated with growth inhibition of human colon, breast, ovarian, and gastric cancer cells in vitro, accompanied by a reduction in VEGF, bFGF, and TGF-α production and substantially reduced tumor microvessel density (Ciardiello et al. 2000). Gefitinib prevents EGF-induced upregulation of VEGF and IL-8, restricts EGF-induced endothelial cell migration and tube formation in vitro, and inhibits neovascularization in a mouse cornea model (Hirata et al. 2002). In cultured human squamous carcinoma cells, gefitinib inhibits molecular pathways involved in cell migration and invasiveness, thereby reducing the ability of cells to invade a complex extracellular matrix (Barnes et al. 2003).

**Erlotinib**

Erlotinib hydrochloride (Tarceva), formerly known as CP-358,744 and subsequently as OSI-774, is a potent and reversible quinazoline-type inhibitor of human EGFR tyrosine kinase in the nanomolar range. Erlotinib inhibits proliferation of DiFi human colon tumor cells at submicromolar concentrations in cell culture, blocks cell-cycle progression at the G1 phase and triggers apoptosis (Moyer et al. 1997). At doses of 100 mg/kg, erlotinib completely prevents EGF-induced phosphorylation of EGFR in human HN5 tumor xenografts in athymic mice and of hepatic EGFR of the treated mice (Moyer et al. 1997). Substantial growth inhibition of human tumor xenografts in athymic mice is achieved with lower oral doses of the agent with an ED₉₀ of 10 mg/kg daily for a 20-day treatment period (Pollack et al. 1999). Combination chemotherapy of erlotinib with cisplatin produces a significant response greater than that of cisplatin alone, with no detected effects on body weight or lethal toxicity.

*In vitro* and *in vivo* studies have shown that erlotinib has activity against human colorectal, head and neck, NSCLC and pancreatic tumor cells (Akita & Sliwkowski 2003). Recent preclinical studies suggest that erlotinib may also have activity against tumors that are dependent on HER2 activation for growth and/or survival. In preclinical studies, combining erlotinib with cisplatin, doxorubicin, gemcitabine or low-dose paclitaxel had an additive effect on antitumor activity with no increase in toxicity (Akita & Sliwkowski 2003). Submicromolar concentrations of erlotinib can specifically inhibit mutant EGFRvIII transformed cells (Iwata et al. 2002). This is noteworthy because EGFRvIII is prevalent in a high percentage of glial tumors (Jungluth et al. 2003).

**Other TKIs**

Other TKI agents in clinical development include the irreversible pan-erbB inhibitor canertinib (CI-1033; Pfizer), EKB-569 (Wyeth Ayerst), GW572016 (GlaxoSmithKline), and the pyrrolopyrimidine compound, PKI-166 (Novartis). In contrast to the mAbs, TKIs do not elicit an immune response. They do appear to inhibit internalization of EGF receptors. A recent study demonstrated that the EGFR-specific TKI, PD158780, inhibits the recruitment of EGFR to clathrin-coated pits, the first stage in receptor endocytosis (Sorkina et al. 2002). Unlike the mAbs, TKIs show

### Table 3 TKIs in clinical trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
<th>Generic/trade name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZD1839</td>
<td>erbB1</td>
<td>Gefitinib/Iressa</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>OSI-774</td>
<td>erbB1</td>
<td>Erlotinib HC1/Tarceva</td>
<td>OSI/Genentech/Roche</td>
</tr>
<tr>
<td>CI-1033</td>
<td>pan erbB</td>
<td>Canertinib</td>
<td>Pfizer</td>
</tr>
<tr>
<td>EKB-569</td>
<td>erbB1/2</td>
<td>—</td>
<td>Wyeth Ayerst</td>
</tr>
<tr>
<td>GW2016</td>
<td>erbB1/2</td>
<td>—</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>PKI-166</td>
<td>erbB1/2</td>
<td>—</td>
<td>Novartis</td>
</tr>
</tbody>
</table>

*Approved.*
activity against other receptors such as HER2 at high concentrations (gefitinib and erlotinib) or all four HER (erbB) receptors as in the case of canertinib. The clinical significance of the differences in activity between mAbs to EGFR and the TKI compounds is not yet clear. The agents furthest along in clinical development, gefitinib and erlotinib, are used in this review as examples of TKIs with specificity for EGFR.

Clinical activity of EGFR inhibitors

The mAbs such as cetuximab and ABX-EGF, and TKIs such as gefitinib and erlotinib display markedly different pharmacokinetic (PK) profiles, and these compounds differ in their route and frequency of administration. These characteristics have important implications for patient convenience on the one hand, and for safety characteristics on the other. As proteins, cetuximab and ABX-EGF are subject to degradation in the digestive system and must, therefore, be administered by i.v. injection. In contrast, gefitinib and erlotinib are administered orally, a potential advantage for chronic therapy (Baselga et al. 2002). On the other hand, the TKIs need to be administered daily, and oral dosing is associated with dose-limiting gastrointestinal toxicity (Albanell et al. 2001). The mAbs do not appear to induce significant diarrhea because of their mode of delivery and inability to cross basement membranes into the lumen of the gastrointestinal tract (Herbst & Hong 2002). However, the large size of these macromolecules may limit their ability to penetrate easily into some anatomical compartments, such as the central nervous system.

Cetuximab, ABX-EGF, gefitinib, and erlotinib have all been evaluated in clinical trials both as single agents and in combination with conventional chemotherapy or radiation therapy. Because EGFR inhibition and conventional anticancer therapy act via different cytotoxic mechanisms, combination therapy offers the potential advantages of additive or synergistic activity without overlapping toxicity profiles (Kim et al. 2001). Numerous preclinical studies have demonstrated additive or synergistic antitumor activity, both in vitro and in vivo.

Treatment with cetuximab, ABX-EGF, gefitinib or erlotinib is commonly associated with the development of an aceneiform rash, generally involving the face, neck and upper torso. The rash is typically mild (grade 1-2), does not require dose adjustment, and resolves or stabilizes with continued treatment. This cutaneous effect appears to be a direct biological response to EGFR inhibition (Busam et al. 2001), and there is suggestive evidence that development of an aceneiform rash may be predictive of an ultimate response to therapy (Kies et al. 2002, Cohen 2003). Indeed, the presence and intensity of skin rash was found to correlate with increased survival in several clinical trials across multiple malignancies (Saltz et al. 2003).

Cetuximab

Cetuximab is administered i.v. at doses of 200-400 mg/m² and has a mean half-life of 114 h (range 75-188 h), thus allowing weekly administration. The kinetics of cetuximab are nonlinear, with complete saturation of systemic clearance, and are unaffected by co-administration with cisplatin (Baselga 2001). In three phase I studies of patients with cancer of the head and neck or NSCLC, a loading dose of 400 mg/m² of cetuximab and a weekly maintenance dose of 250 mg/m² was associated with near complete saturation of EGFR within the tumor, an important criterion for optimal activity (Baselga et al. 2000). Adverse effects were minimal and a maximum tolerable dose (MTD) was not reached. Antibodies against cetuximab were detected in only one patient out of a total of 52 subjects treated. The PK profile of cetuximab does not change following repeated doses, confirming a lack of immunogenicity (Mendelsohn 2001). Subsequent clinical trials have been conducted using this dosing regimen.

Several phase I and I/II studies were undertaken to investigate the tolerability of cetuximab in combination with conventional cytotoxic agents such as cisplatin or carboplatin and 5-fluorouracil (5FU) in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) (Vega-Villegas et al. 2003), gemcitabine/carboplatin in chemotherapy-naive patients with advanced stage IV NSCLC (Robert et al. 2003), paclitaxel and carboplatin in previously untreated patients with stage IV NSCLC (Kelly et al. 2003), or cetuximab in combination with chemotherapy or radiotherapy (Robert et al. 2001, Needle 2002). In these studies, the most common toxicity associated with cetuximab was aceneiform rash (mainly grade 1–2) and the most common grade 3 toxicity was fatigue. Allergic/hypersensitivity reactions were less common. A series of studies (phases I–III) of cetuximab+cisplatin or carboplatin in SCCHN have shown that toxicities are generally nonoverlapping (Shin et al. 2001, Baselga et al. 2002, Burtness et al. 2002, Kies et al. 2002). Various studies that have been carried out with cetuximab, either as monotherapy or in combination with conventional therapy, are summarized in Table 4.

The US product labeling for cetuximab (Erbitux) in the treatment of irinotecan-refractory colorectal cancer describes the risk of severe infusion reactions (3% of patients), 90% of these being associated with the first infusion. It is rarely fatal (<1 in 1000). As with gefitinib (Iressa, see below) and conventional cancer therapy, there is a potential risk of developing interstitial lung disease...
Table 4 Cetuximab clinical trials

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>No. subjects</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>TTP</th>
<th>OS</th>
<th>Remarks</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;N</td>
<td>424</td>
<td>+Radiation</td>
<td>–</td>
<td>–</td>
<td>54 months</td>
<td>Positive phase III trial</td>
<td>Bonner et al. (2004)</td>
</tr>
<tr>
<td>H&amp;N or NSCLC</td>
<td>52</td>
<td>Monotherapy</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3×Phase I</td>
<td>Baselga et al. (2000)</td>
</tr>
<tr>
<td>SCCHN</td>
<td>15</td>
<td>Monotherapy</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Phase I</td>
<td>Robert et al. (2001)</td>
</tr>
<tr>
<td>SCCHN</td>
<td>22</td>
<td>+Cisplatin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td>Phase IB Shin et al. (2001)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>41</td>
<td>+Gemcitabine</td>
<td>12</td>
<td>4 months</td>
<td>–</td>
<td>Gemcitabine TTP=9 weeks</td>
<td>Abbruzzese et al. (2001)</td>
</tr>
<tr>
<td>SCCHN</td>
<td>96</td>
<td>+Cisplatin/carboplatin</td>
<td>14.6</td>
<td>66 days</td>
<td>6 months</td>
<td>responders: OS=269 days</td>
<td>Baselga et al. (2002)</td>
</tr>
<tr>
<td>SCCHN</td>
<td>44</td>
<td>+Cisplatin</td>
<td>13.7</td>
<td>–</td>
<td>7 months</td>
<td></td>
<td>Burtness et al. (2002)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>61</td>
<td>+Cisplatin/vinorelbine</td>
<td>53</td>
<td>–</td>
<td>–</td>
<td>Chemotherapy only ORR=32%</td>
<td>Gatzemeier et al. (2003)</td>
</tr>
<tr>
<td>SCCHN</td>
<td>79</td>
<td>+Cisplatin</td>
<td>11.5</td>
<td>–</td>
<td>–</td>
<td>Skin rash +ve: ORR=15.1%</td>
<td>Kies et al. (2002)</td>
</tr>
<tr>
<td>CRC</td>
<td>57</td>
<td>Monotherapy</td>
<td>11</td>
<td>–</td>
<td>–</td>
<td>Irinotecan refractory</td>
<td>Saltz et al. (2003)</td>
</tr>
<tr>
<td>CRC</td>
<td>25</td>
<td>+Irinotecan; 5FU; LV</td>
<td>44</td>
<td>–</td>
<td>–</td>
<td>untreated, metastic</td>
<td>Rosenberg et al. (2002)</td>
</tr>
<tr>
<td>CRC</td>
<td>18</td>
<td>+Irinotecan; FA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Metastatic</td>
<td>Schoffski et al. (2002)</td>
</tr>
<tr>
<td>Nasopharyngeal</td>
<td>53</td>
<td>Monotherapy</td>
<td>17.0</td>
<td>–</td>
<td>–</td>
<td>Metastatic; failed platinum therapy</td>
<td>Chan et al. (2003)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>31</td>
<td>+Paclitaxel; carboplatin</td>
<td>29</td>
<td>4.5 months</td>
<td>16 months</td>
<td>Stage IV; phase I/II study</td>
<td>Kelly et al. (2003)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>47</td>
<td>+Docetaxel</td>
<td>28</td>
<td>89 days</td>
<td>–</td>
<td></td>
<td>Kim et al. (2002)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>35</td>
<td>+Gemcitabine/carboplatin</td>
<td>28.6</td>
<td>5.5 months</td>
<td>10 months</td>
<td>Stage IV; phase IB/IIA</td>
<td>Robert et al. (2003)</td>
</tr>
<tr>
<td>CRC</td>
<td>329</td>
<td>±Irinotecan</td>
<td>23/11</td>
<td>4/1.5 months</td>
<td>9/7 months</td>
<td>Irinotecan refractory</td>
<td>Cunningham et al. (2003)</td>
</tr>
</tbody>
</table>

ORR, overall response rate; TTP, time to progression; OS, overall survival; H&N, head and neck; NSCLC, non-small-cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; CRC, colorectal cancer.
radiation phase III clinical trial of 424 patients who received oxaliplatin (FOLFOX) vs FOLFOX only. positive colorectal cancer, will evaluate cetuximab initiation. Another US phase III trial (the EXPLORE metastatic EGFR-positive colorectal cancer, has been can vs irinotecan, as second-line treatment in patients with epidermal growth factor receptor (EGFR) inhibition. This finding will likely stimulate many new clinical trials for other cancer types in which radiation plays a central treatment role.

ABX-EGF
PK and pharmacodynamic studies were conducted with i.v. ABX-EGF to determine optimal dosing in cancer patients. Saturation of EGFR was assessed by clearance and the incidence and severity of the characteristic acneiform rash. In a phase I trial, 43 patients with renal, prostate, NSCLC, pancreatic, gastroesophageal or colorectal cancer received ABX-EGF weekly for up to 4 weeks at doses up to 2.5 mg/kg (Roskos et al. 2002). All patients who received doses of 2 or 2.5 mg/kg ABX-EGF developed rashes that resolved within 4 weeks of the last dose. No human anti-human antibodies (HAHAs) were detected in any patient and no alterations in PK occurred in any subject, consistent with the absence of HAHA development. It was concluded that the low PK variability, absence of immunogenicity, and high potency of ABX-EGF permitted dosing up to 2.0–2.5 mg/kg, producing evidence of EGFR blockade (acneiform rash) while maintaining a tolerable safety profile. In another phase I trial, excluding skin rash, the most common grade 2 or higher adverse events reported were asthenia and back pain (each 15%), followed by unspecified pain (13%). Diarrhea was minimal (7%; grade 1–2) and not dose-related. There was no anaphylaxis and no allergic or infusion-related reactions were observed (Figlin et al. 2002).

A two-part, phase II monotherapy trial of eight weekly i.v. infusions of ABX-EGF was conducted in patients with renal cell carcinoma in whom IL-2/interferon-α treatment failed or who were not able to receive this treatment (Schwartz et al. 2002). Stable or responding patients were eligible for extended weekly treatment, at the assigned dose (1.0, 1.5 or 2.0 mg/kg), for 8 additional months or until disease progression. At the time of report, 58 patients had been treated and 32 had completed one 8-week cycle. Two objective responses were seen at doses of 1.0 and 1.5 mg/kg. Minor response or stable disease was observed in 38% of patients, while 36% had progressive disease. Grade 2/3 adverse events were skin rash, pruritus, dyspnea, fatigue, diarrhea,
abdominal pain, nausea and vomiting. Acneiform rash (grades 1 and 2) was the most frequently observed adverse event (61%). In the same series of patients, when the dosage was increased to 2.5 mg/kg (21 patients) the incidence of skin rash increased to 100% (Schwartz et al. 2002). No HAHA’s were detected.

A multicenter trial of ABX-EGF monotherapy was conducted in patients with metastatic colorectal cancer (Mepol et al. 2003). At the time of report, 44 patients had received treatment (2.5 mg/kg, i.v. for 1 h, weekly for 3 weeks). Maximum rash intensity was generally achieved by week 3 of treatment. There were no complete responses, 9% of subjects showed a partial response, there was stable disease in 52%, and progressive disease in 39% of patients. There were no cases of anaphylaxis, other allergic reactions, or medically significant transfusion reactions, and no incidence of HAHA response.

Abgenix, in collaboration with Amgen Inc., are conducting phase II trials of ABX-EGF monotherapy in hormone-resistant prostate cancer patients, single-arm combination therapy (first-line treatment) in colorectal cancer, and two-arm combination ABX-EGF + chemotherapy vs chemotherapy alone (first-line treatment) in NSCLC.

**Gefitinib**

Following a single oral dose of up to 700 mg gefitinib in both healthy volunteers and patients with advanced malignancies, peak plasma drug concentration was attained at 3–7 h, with an elimination half-life of approximately 48 h (Baselga & Averbuch 2000). Daily oral administration to cancer patients results in a 2-fold accumulation of drug compared with a single-dose administration and steady-state plasma concentrations are achieved within 10 days. Long-term administration of gefitinib was generally well tolerated at doses up to 600 mg/day. Higher doses were associated with dose-limiting toxicities, such as grade 3 diarrhea (Ranson et al. 2002). The gastrointestinal toxicity of gefitinib appears to reflect the direct exposure of intestinal epithelial cells to EGFR inhibition via oral administration.

As with cetuximab, gefitinib labeling carries a warning concerning pulmonary toxicity (ILD). The overall incidence is about 1%, with approximately one-third of cases being fatal (AstraZeneca Pharmaceuticals LP 2003). This warning was included as a result of post-approval experience in Japan where a small proportion of patients (170 out of 10 000 (1.7%)) receiving the drug developed fatal ILD (Schultz 2003). Although worthy of careful evaluation, it should be noted that ILD is also seen in patients with advanced lung cancer treated by conventional chemotherapy or radiotherapy. Other precautions concern the potential for hepatic toxicity due to asympeto-
<table>
<thead>
<tr>
<th>Cancer type</th>
<th>No. subjects</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>TTP</th>
<th>OS</th>
<th>Remarks</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various or healthy</td>
<td>96</td>
<td>Dose escalation to 700 mg</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Baselga et al. (2002)</td>
</tr>
<tr>
<td>Solid malignancies</td>
<td>64</td>
<td>50–950 mg/day</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NSCLC 4/16 ORR 300–700 mg/day</td>
<td>Ransom et al. (2002)</td>
</tr>
<tr>
<td>SCCHN</td>
<td>40</td>
<td>500 mg/day</td>
<td>20</td>
<td>–</td>
<td>8 months</td>
<td>–</td>
<td>Cohen et al. (2003a)</td>
</tr>
<tr>
<td>SCCHN</td>
<td>14</td>
<td>250 mg/day</td>
<td>11</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Cohen et al. (2003b)</td>
</tr>
<tr>
<td>Renal cell</td>
<td>16</td>
<td>500 mg/day</td>
<td>0</td>
<td>3.7 months</td>
<td>–</td>
<td>–</td>
<td>Drucker et al. (2003)</td>
</tr>
<tr>
<td>Renal cell</td>
<td>21</td>
<td>500 mg/day</td>
<td>5</td>
<td>–</td>
<td>8 months</td>
<td>–</td>
<td>Dawson et al. (2003)</td>
</tr>
<tr>
<td>Breast</td>
<td>31</td>
<td>500 mg/day</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Baselga et al. (2003)</td>
</tr>
<tr>
<td>Breast</td>
<td>68</td>
<td>250 mg/day</td>
<td>63</td>
<td>–</td>
<td>–</td>
<td>+Paclitaxel/carboplatin</td>
<td>Fountzilas et al. (2003)</td>
</tr>
<tr>
<td>Cervical</td>
<td>15</td>
<td>500 mg/day</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Viens et al. (2003)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>210</td>
<td>250/500 mg/day</td>
<td>18/19</td>
<td>2.8 months</td>
<td>8 months</td>
<td>IDEAL-1 trial</td>
<td>Fukuoka et al. (2003)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>216</td>
<td>250/500 mg/day</td>
<td>11</td>
<td>3–7 months</td>
<td>6 months</td>
<td>IDEAL-2 trial</td>
<td>Kris et al. (2003)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1093</td>
<td>250/500 mg/day± chemotherapy</td>
<td>–</td>
<td>–</td>
<td>10/10 months</td>
<td>INTACT-1 trial</td>
<td>Giaccone et al. (2002)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1037</td>
<td>250/500 mg/day± chemotherapy</td>
<td>–</td>
<td>–</td>
<td>10/9 months</td>
<td>INTACT-II trial</td>
<td>Johnson et al. (2002)</td>
</tr>
<tr>
<td>CRC</td>
<td>?</td>
<td>? mg/day±FOLFOX</td>
<td>75</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Cho et al. (2003)</td>
</tr>
</tbody>
</table>

ORR, overall response rate; TTP, time to progression; OS, overall survival; NSCLC, non-small-cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; CRC, colorectal cancer; IDEAL, Iressa Dose Evaluation in Advanced Lung Cancer; INTACT, Iressa NSCLC Trial Assessing Combination Treatment; FOLFOX, 5-Fluorouracil/leucovorin and oxaliplatin.
was considered acceptable. However, no improvement was observed relative to placebo in overall survival, progression-free survival, time to worsening of symptoms, objective tumor response, QOL, or safety (Giaccone et al. 2002, Johnson et al. 2002, Saul 2003). The INTACT trials were well designed and the results were considered definitive (Saul 2003).

The reason for the failure of gefitinib to show clinical advantage in combination with chemotherapy in lung cancer remains unclear. Multivariate analysis of prognostic factors for overall survival in INTACT-1 and INTACT-2 trial data did not show any consistent effect of gefitinib combined with chemotherapy, compared with chemotherapy alone, on any known prognostic factors for survival outcome in advanced NSCLC (Giaccone et al. 2003). Furthermore, post hoc subset analysis did not reveal any susceptible subpopulations (Herbst 2003). Furthermore, post hoc subset analysis did not reveal any susceptible subpopulations (Herbst 2003). Some authors have argued that these phase III studies had a ‘fatal flaw’ in their design by not requiring study subjects to show positive EGFR status (Dancey & Freidlin 2003). However, a definitive correlation between EGFR status (Dawson et al. 2003), or that of other biological markers (Baselga et al. 2003), and response to gefitinib treatment (or other EGFR inhibitors) has yet to be demonstrated. This relationship is being more systematically investigated using 732 tumor samples collected during the two INTACT trials (Giaccone et al. 2003).

Erlotinib

The pharmacokinetics of erlotinib are dose-dependent, and repetitive daily treatment does not result in drug accumulation when administered at an average dosage of 150 mg/day. The elimination half-life averages approximately 24 h (Hidalgo et al. 2001). Plasma concentrations exceeded those that were associated with activity in preclinical models. The principal dose-limiting toxicities in phase I trials of erlotinib were acneiform rash and diarrhea (Grunwald & Hildago 2003b). In a phase I study of erlotinib in patients with advanced solid malignancies, no severe toxicities prevented dose escalation from 25 up to 100 mg/day. However, the incidence of severe diarrhea and/or cutaneous toxicity was unacceptably high at erlotinib doses exceeding 150 mg/day administered once daily for 3 weeks, every 4 weeks (Hidalgo et al. 2001). The diarrhea was considered dose limiting at 200 mg/day but was less frequent at 150 mg/day and manageable at this dose with loperamide. Based on these provisional data, 150 mg/day was selected as the MTD for the phase II program (Herbst 2003b).

Erlotinib has been evaluated alone vs in combination therapy with temozolomide in a phase I study of patients with malignant glioma (Prados et al. 2003). Concomitant use of enzyme-inducing epileptic drugs reduced exposure of the patient to erlotinib and its active metabolite. The objective responses were encouraging, and a corresponding phase II study was initiated. A phase IIB trial of escalating doses of erlotinib in combination with a standard dose gemcitabine regimen was conducted in patients with advanced pancreatic adenocarcinoma and other malignancies potentially responsive to gemcitabine (Dragovich et al. 2003). Preliminary results indicated some activity and no serious toxicities at dosages of 100 or 250 mg/day of erlotinib, although one patient with lung cancer developed fatal pulmonary toxicity, which was attributed to gemcitabine treatment and prior radiotherapy. This combination is being compared with standard gemcitabine therapy in a phase III randomized trial initiated by the National Cancer Institute of Canada, as described below.

Preliminary results from a phase II trial of erlotinib in patients with bronchioloalveolar cell carcinoma (BAC) were recently reported (Miller et al. 2003). A total of 33 patients with proven BAC or a variant had been treated at the time of the report. The authors concluded that erlotinib is an active agent in this disease and, if this is confirmed with additional patient accrual, a follow-up phase III trial is planned. A possible difference in responsiveness to the drug between smokers and non-smokers is being investigated.

Two phase III trials of erlotinib (150 mg/day) + chemotherapy were conducted in patients with first-line metastatic NSCLC. These trials, which have similar protocols, are called TRIBUTE (Herbst et al. 2004) in the United States, and TALENT outside of the United States (Gatzemeier et al. 2004). As with the INTACT trials with gefitinib in NSCLC, neither of these erlotinib trials met the primary endpoint of improving overall survival. In the TRIBUTE study, one of the secondary endpoints, time to symptomatic progression, did achieve statistical significance but this did not translate into improvement in overall survival or time to disease progression. The addition of erlotinib to chemotherapy was generally well tolerated and there were no unexpected toxicities. The results, while disappointing, were not entirely unexpected in view of the failure of the gefitinib trials in the same clinical setting.

A 700-patient, randomized, phase III trial of erlotinib monotherapy (150 mg/day) vs placebo in second- or third-line metastatic NSCLC completed enrollment in January 2003. This study was conducted by OSI Pharmaceuticals in collaboration with the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). Although the addition of erlotinib to doublet chemotherapy regimens in advanced lung cancer failed to identify a survival advantage over chemotherapy alone, this new study met the primary endpoint of improving overall survival from 4.7 to 6.7 months, as well as secondary endpoints of...
### Table 6 Erlotinib clinical trials

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>No. subjects</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>TTP</th>
<th>OS</th>
<th>Remarks</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid malignancies</td>
<td>18</td>
<td>Dose escalation to 1000 mg/week</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Pharmacological study</td>
<td>Karp et al. (2000)</td>
</tr>
<tr>
<td>Solid malignancies</td>
<td>40</td>
<td>Dose escalation to 200 mg/week</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Phase I/pharmacological study</td>
<td>Hildago et al. (2001)</td>
</tr>
<tr>
<td>SCCHN</td>
<td>114</td>
<td>150 mg/day</td>
<td>–</td>
<td>9.6 weeks</td>
<td>6.0 months</td>
<td>Phase II. 4.3% PR, 38.3% SD</td>
<td>Herbst (2003b), Soulieres et al. (2004)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>34</td>
<td>150 mg/day</td>
<td>–</td>
<td>77 days</td>
<td>–</td>
<td>Phase II</td>
<td>Herbst (2003b)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>17</td>
<td>100 or 150 mg/day</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+Gemcitabine, accruing</td>
<td>Dragovich et al. (2003)</td>
</tr>
<tr>
<td>BAC</td>
<td>33</td>
<td>?</td>
<td>27</td>
<td>–</td>
<td>–</td>
<td>Accruing</td>
<td>Miller et al. (2003)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>57</td>
<td>150 mg/day</td>
<td>12.3</td>
<td>–</td>
<td>8.4 months</td>
<td>Phase II. 8.8% PR, 38.6% SD</td>
<td>Perez-Soler et al. (2003), Herbst (2003b)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1059</td>
<td>150 mg/day</td>
<td>5</td>
<td>5.1 months</td>
<td>10.8 months</td>
<td>+Paclitaxel/carboplatin. TALENT</td>
<td>Herbst et al. (2004)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1172</td>
<td>150 mg/day</td>
<td>–</td>
<td>167 days</td>
<td>301 days</td>
<td>+Paclitaxel/carboplatin. TRIBUTE</td>
<td>Gatzemeier et al. (2004)</td>
</tr>
<tr>
<td>Glioma</td>
<td>47</td>
<td>Dose escalation to 400 mg/day</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Accruing</td>
<td>Prados et al. (2003)</td>
</tr>
</tbody>
</table>

ORR, overall response rate; TTP, time to progression; OS, overall survival; NSCLC, non-small-cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; BAC, bronchioalveolar cell carcinoma; PR, partial response; SD, stable disease.
improving time to symptomatic progression, progression-free survival and response rate (Shepherd et al. 2004). Additionally, OSI Pharmaceuticals and Genentech have initiated a randomized, placebo-controlled, phase III trial evaluating erlotinib in combination with gemcitabine in 450 patients with previously untreated metastatic pancreatic cancer; again in collaboration with the NCIC CTG.

Figure 3 Mutations identified in the EGFR tyrosine kinase domain (red) conferring sensitivity to gefitinib in non-small cell lung cancer patients. Adapted with permission from Lynch et al. (2004).

Discussion

Molecular inhibitors of EGFR signaling represent a highly promising class of molecular targeted anticancer agents. A series of EGFR inhibitors from both the mAb and TKI class have demonstrated clear clinical activity as monotherapy in the treatment of refractory solid malignancies. Gefitinib has received approval for refractory NSCLC in several countries, including the United States (FDA approval May 2003). Cetuximab has also received recent FDA approval in the United States (February 2004) and Switzerland for colorectal cancer that is unresponsive to irinotecan. Preliminary reports regarding the capacity of erlotinib to extend overall survival in advanced, recurrent NSCLC patients suggest that this small molecule EGFR inhibitor may also gain FDA approval in the future months. If so, this would represent the third molecular inhibitor of EGFR signaling to gain FDA approval in cancer therapy over the last 12-18 months, validating a central role of EGFR as an important molecular target in human epithelial tumors.

Despite the recent success of EGFR inhibitory agents in gaining FDA approval, there remain several major gaps in our knowledge regarding the function, activity and preferred clinical applications for EGFR inhibitors. The preclinical data regarding EGFR inhibitors have been exceptionally strong, but not fully predictive of clinical trial results. Indeed, preclinical studies predicted a highly favorable interaction of EGFR inhibition combined with cytotoxic chemotherapy in NSCLC that was not substantiated in major lung cancer trials such as the INTACT and TALENT/TRIBUTE trials with gefitinib and erlotinib respectively. It remains to be clarified whether these results reflect a generic adverse interaction between EGFR inhibitors and concurrent cytotoxic chemotherapy in lung cancer, or whether this reflects inadequate patient selection in the absence of defined parameters that can better predict those patients likely to respond favorably to EGFR inhibitors. With regard to patient selection, brand new reports suggest that a subgroup of patients with lung cancer carry specific mutations (Fig. 3) in the EGFR gene which correlate with the likelihood of response to the EGFR inhibitor gefitinib (Lynch et al. 2004, Paez et al. 2004). This type of finding offers future potential to more accurately screen and predict responders for specific EGFR inhibitors.

The rational selection of cancer patients for EGFR inhibitor therapies remains a major challenge. Unlike the use of Herceptin in breast cancer therapy, where the link between overexpression of the molecular target (erbB-2) and response to therapy is relatively clear, the association between EGFR overexpression and response to EGFR inhibitor therapy does not appear straightforward. The complexity of the erbB signaling network and the
The impact of EGFR inhibitors in cancer therapy will ultimately reflect the overall importance of the EGFR as a molecular target in human malignancy. For those patients (individual tumors) in which EGFR signaling represents a dominant driving force for tumor progression, EGFR inhibitor strategies will likely prove of considerable value. However, for those patients (tumors) in which EGFR signaling represents just one of several aberrant molecular growth pathways conferring growth advantage, it would seem unlikely that EGFR inhibition strategies alone will provide substantial therapeutic benefit. In this regard, preclinical studies and innovative clinical trial designs are beginning to examine the capacity of multiple molecular targeted agents to work in concert to achieve tumor regression. Studies to more thoroughly examine optimal sequencing strategies between EGFR inhibitors and cytotoxic therapies such as radiation and chemotherapy are developing. As our understanding regarding mechanisms of actions for EGFR molecular inhibitors increases, more rational clinical designs which examine EGFR inhibitors combined with radiation and chemotherapy will emerge. In parallel, our ability to select patients (tumors) whose molecular profile renders them likely to respond to specific EGFR inhibitory strategies will mature.

Acknowledgement

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