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EGFR Inhibition in the Treatment of Non-Small Cell Lung Cancer

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Abstract

Epidermal growth factor receptor (EGFR) inhibitors have introduced the concept of targeted therapy to the treatment of non-small cell lung cancer (NSCLC). These agents appear most effective in patients with tumors that are highly dependent on EGFR signaling pathways, a population that disproportionately includes females, nonsmokers, individuals of East Asian origin, and patients with adenocarcinoma histology. Currently available EGFR-inhibiting drugs include the tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, and lapatinib, which are administered orally and interfere with the intracellular tyrosine kinase domain, and the monoclonal antibodies (mAbs) cetuximab and panitumumab, which are administered intravenously and interfere with extracellular ligand binding. While the use of EGFR TKIs as monotherapy prolongs survival in metastatic NSCLC, they have demonstrated no benefit when added to conventional, cytotoxic chemotherapy. In contrast, the anti-EGFR mAb cetuximab appears most effective when combined with chemotherapy or radiation. Despite dramatic initial responses to treatment in some cases, NSCLC eventually becomes resistant to EGFR inhibition. Possible mechanisms include secondary mutations that interfere with drug binding, oncogenic pathways driven by other receptor tyrosine kinases, and independent activity of downstream signaling molecules. Efforts to overcome such resistance include irreversibly binding EGFR TKIs, multi-targeted TKIs, and combinations with chemotherapy, radiation, and other targeted therapies.

Keywords

non-small cell lung cancer; epidermal growth factor receptor; monoclonal antibodies; tyrosine kinase inhibitors; targeted therapy

INTRODUCTION

To understand the impact of epidermal growth factor receptor (EGFR) inhibition on the treatment of non-small cell lung cancer (NSCLC), one must consider the state of NSCLC at the close of the twentieth century. While declining tobacco use in the United States had led to a plateau in new cases, rising smoking rates in developing countries were fueling an increased incidence worldwide. The effectiveness of radiographic screening for lung cancer remained disputed [Henschke et al., 2006]. Almost 75% of patients presented with advanced, inoperable disease. With standard first-line platinum-based chemotherapy, response rates were approximately 20%; median survival, approximately 9 months [Schiller et al., 2002]. Second-line treatment regimens, incorporating drugs such as the antimetabolite pemetrexed or the microtubule inhibitor docetaxel, yielded significant toxicity but response rates under 10%

[Shepherd et al., 2000]. Third-line chemotherapy, when employed, led to responses in about 2% of patients [Massarelli et al., 2003]. Lung cancer remained the number one cancer killer in both men and women.

While the treatment of advanced lung cancer has progressed relatively little, the treatment of other malignancies had benefited from recent biologic insights. Imatinib, an inhibitor of the fusion protein BCR-ABL, revolutionized the treatment of chronic myelogenous leukemia [Kantarjian et al., 2002]. Rituximab, an antibody directed against the B-cell marker CD20, significantly improved outcomes when added to standard chemotherapy for the treatment of B-cell non-Hodgkin's lymphoma [Coiffier et al., 2002]. These targeted therapies proved not only effective, but also better tolerated than traditional cytotoxic chemotherapy.

EGFR inhibition has introduced targeted therapy to the treatment of NSCLC. In so doing, it has raised new issues of patient selection and clinical trial design, impacted the assessment of drug efficacy, and expanded the patient population eligible for anti-cancer therapy. Additionally, the growing understanding of EGFR tyrosine kinase mutations, which appear unique to NSCLC, has highlighted the clinical importance of tumor molecular characteristics in this era of new cancer treatments. To offer insight into the use of EGFR inhibition for NSCLC treatment, this paper reviews EGFR biology, classes of EGFR inhibiting drugs, molecular predictors of EGFR efficacy, clinical trials of EGFR inhibitors, and mechanisms of tumor resistance to EGFR.

EGFR BIOLOGY

EGFR, also known as HER1 (human epidermal growth factor receptor 1) or ErbB1, belongs to a 4-member family of receptor tyrosine kinases. EGFR has an extracellular ligand-binding domain (621 amino acids), a transmembrane anchoring region (23 amino acids), and an intracellular tyrosine kinase (542 amino acids). After binding of ligand such as epidermal growth factor [EGF], transforming growth factor [TGF], and others, receptor subunits dimerize, which leads to autophosphorylation of intracellular tyrosine residues (see Figure 1). This action creates docking sites for numerous intracellular effector proteins, thereby generating multiple signal transduction cascades. These include the Ras-Raf-MEK (mitogen-activated and extracellular-signal regulated kinase kinase), PI3K (phosphatidylinositol-3 kinase)-Akt, and STAT (signal transducer and activator of transcription) pathways (see Fig. 1). Ultimately, these molecular signals result in cellular proliferation, resistance to apoptosis, cellular invasion, metastasis, and angiogenesis [Schreiber et al., 1986; Petit et al., 1997; Gibson et al., 1999; Modjtahedi et al., 2000; Harari et al., 2007]. Independent of kinase-dependent signal-transduction pathways, the EGFR complex may also be internalized and translocate to the nucleus, where it modifies gene transcription and contributes to DNA repair mechanisms [Lin et al., 2001; Dittmann et al., 2005].

EGFR is present on normal epithelial cells and a variety of cancer cells. EGFR protein overexpression or *EGFR* gene amplification, mutation, or rearrangement have been demonstrated in multiple malignancies, including cancers of the head and neck, ovary, cervix, bladder, prostate, ovary, esophagus, stomach, brain, breast, endometrium, colon, and lung [Salomon et al., 1995; Krause and Van Etten, 2005]. EGFR is detectable in up to 90% of cases of NSCLC [Rusch et al., 1993; Dutu et al., 2005]. EGFR expression frequently conveys a more aggressive phenotype and worse prognosis. This association has been demonstrated in bladder, breast, and head and neck cancers, as well as NSCLC [Rubin Grandis et al., 1998; Nicholson, Gee et al., 2001; Ohsaki et al., 2000; Hirsch et al., 2003].

EGFR-INHIBITING DRUGS: TYROSINE KINASE INHIBITORS AND MONOCLONAL ANTIBODIES

The two primary means of inhibiting the EGFR pathway are small molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs). EGFR TKIs (molecular weight 400–500 daltons) exert their effects intracellularly. They bind competitively to the adenosine triphosphate pocket of EGFR, inhibiting EGFR autophosphorylation and downstream signal transduction. Anti-EGFR mAbs (molecular weight approximately 150,000 daltons) act extracellularly, antagonizing ligand-receptor binding. This, in turn, prevents receptor subunit dimerization, EGFR autophosphorylation, and signal transduction. Both EGFR TKIs and anti-EGFR mAbs may provide a predominantly cytostatic effect, requiring researchers and clinicians to consider tumor stabilization, in addition to tumor shrinkage, when assessing treatment efficacy.

While the overarching biologic effect—inhibition of EGFR signaling—of these two drug classes is similar, a number of functional distinctions may explain some of the clinical differences (see Table 1). In addition to blockade of EGFR signaling, anti-EGFR mAbs lead to receptor internalization, degradation, and long-term down-regulation [Prewett et al., 1996; Mendelsohn, 1997; Lilenbaum, 2006]. This process does not occur with currently approved EGFR TKIs, which bind reversibly. Additionally, anti-EGFR mAbs, particularly those of IgG1 isotype, may recruit host immune functions to attack the targeted cancer cell. These functions include antibody-dependent cellular cytotoxicity (ADCC; namely, tumor cell-killing mononuclear cells such as macrophages and natural killer cells) and, to a lesser extent, complement-dependent cytotoxicity.

Currently, there are five FDA-approved drugs that inhibit EGFR: 3 TKIs (erlotinib [Tarceva, Genentech, South San Francisco, CA/OSI Pharmaceuticals, Melville, NY], gefitinib [Iressa, AstraZeneca, Wilmington, DE], and lapatinib [Tykerb, GlaxoSmithKline, Middlesex, England]) and two mAbs (cetuximab [Erbix, ImClone Systems, New York, NY] and panitumumab [Vectibix, Amgen, Thousand Oaks, CA]). Three of these drugs (erlotinib, gefitinib, and cetuximab) have been studied extensively in NSCLC. Erlotinib is indicated for second- or third-line monotherapy for metastatic NSCLC. In the United States, gefitinib is indicated only for NSCLC patients who have previously benefited from gefitinib treatment or in the context of a clinical trial. The FDA retracted its general approval for this drug when a phase III trial failed to demonstrate an overall survival benefit [Thatcher et al., 2005]. Lapatinib is a dual HER1 (EGFR) and HER2/neu inhibitor, and is indicated for the treatment of HER2-positive breast cancer. Cetuximab is a chimeric (2/3 human protein, 1/3 mouse protein) IgG1 mAb. The presence of mouse protein leads to possible acute infusion reactions (hence antihistamine premedication is required) and the generation of human anti-mouse antibodies, which could neutralize the effect of the exogenous, therapeutic antibody. Cetuximab is currently approved for the treatment of colorectal and head and neck cancers. It has also been studied extensively in NSCLC.

Panitumumab is a human (100% human protein) IgG2 mAb approved for the treatment of advanced colorectal cancer. Because of its fully human construct, it is less likely to cause allergic infusion reactions than cetuximab. Its IgG2 isotype makes interaction with host immune functions, such as ADCC, less likely than might occur with an IgG1 mAb. Generally, EGFR-inhibiting drugs are well tolerated, with acneiform rash and diarrhea the primary toxicities of both TKIs and mAbs. Rare cases of interstitial lung disease have also been reported [Inoue et al., 2003]. Significant hypomagnesemia occurs in approximately 10% of patients treated with cetuximab monotherapy [Jonker et al., 2007] and in more than 50% of patients receiving cetuximab plus platinum-based chemotherapy [Butts et al., 2007].

IDENTIFICATION OF THE TARGET POPULATION

An underlying premise of targeted therapy is the identification of a target population. For instance, the use of the hormone receptor tamoxifen is limited to the two-thirds of patients with breast cancer whose tumors express the estrogen receptor and/or the progesterone receptor [Early Breast Cancer Trialists' Collaborative Group, 1998]. Estrogen receptor and progesterone receptor status can be determined using standard immunohistochemistry (IHC) techniques. Imatinib (Gleevec) is an inhibitor of the tyrosine kinase of the fusion protein BCR-ABL (breakpoint cluster region Abelson) and is used in the treatment of chronic myelogenous leukemia. Prior to treatment, the presence of BCR-ABL can be inferred through the detection of the Philadelphia chromosome (t(9;22)), either through cytogenetic analysis (i.e., karyotype), fluorescence in situ hybridization (FISH), or polymerase chain reaction (PCR). In contrast to the relatively straightforward identification of patients likely to benefit from tamoxifen or imatinib, the selection of patients likely to benefit from EGFR-inhibiting drugs remains a complex and disputed process.

Predicting Response to EGFR TKIs: EGFR Mutations, Amplification, and Gene copy number

In early studies of EGFR TKIs, the level of EGFR protein expression in tumor tissue did not appear to correlate with treatment response [Perez-Soler et al., 2004]. Instead, multiple clinical investigators noted that patients most likely to respond to these drugs were females, those with minimal or no smoking history, those of East Asian descent, and those with adenocarcinoma histology (particularly those with bronchioloalveolar features) [Fukuoka et al., 2003; Kris et al., 2003; Janne et al., 2004; Perez-Soler et al., 2004; Kim et al., 2005; Veronese et al., 2005]. Molecular analysis of tumor specimens from these individuals revealed high rates of activating mutations in the EGFR tyrosine kinase domain (centered around exons 18–21) [Kosaka et al., 2004; Lynch et al., 2004; Paez et al., 2004; Pao et al., 2004, 2005a,b; Kobayashi et al., 2005; Kwak et al., 2005]. These mutations hyperactivate the EGFR tyrosine kinase, rendering cancer cells highly dependent on EGFR oncogenic pathways for survival (a concept known as oncogene addiction) [Weinstein, 2002; Weinstein and Joe, 2006; Sharma et al., 2007] and thus exquisitely sensitive to EGFR inhibition.

Exon 19 and exon 21 mutations each account for approximately 45% of *EGFR* gene mutations. Exon 19 mutations, most commonly in-frame deletions of amino acids 747–750, are clustered around the catalytic domain and flank the ATP-binding site. In addition to activating EGFR TK signaling, these structural changes enhance drug binding, resulting in complete blockade of mutated EGFR signaling at relatively low TKI doses [Yun et al., 2007]. Exon 21 mutations, which lie within the TK activation loop, are characteristically L858R substitutions. The remaining 10% of EGFR TK mutations, in exons 18 and 20, do not confer sensitivity to EGFR TKIs and in some cases are associated with resistance (see the section, Resistance to EGFR Inhibition, below).

In NSCLC cases featuring *EGFR* gene mutations, EGFR TKIs have radiographic response rates of over 60%, compared with response rates of approximately 10% in wild-type cases [Bell et al., 2005; Cappuzzo et al., 2005; Han et al., 2005; Mitsudomi et al., 2005; Takano et al., 2005; Sequist et al., 2007; Sequist and Lynch, 2008]. Higher response rates have translated into longer median survival (up to 30 months in some studies) [Cappuzzo et al., 2005; Han et al., 2005; Mitsudomi et al., 2005]. Nevertheless, EGFR mutation status has limited applicability in North America and Western Europe, where only 10% of NSCLC cases have *EGFR* gene mutations, compared with 30–50% of cases in East Asia [Kosaka et al., 2004; Cappuzzo et al., 2005; Chou et al., 2005; Han et al., 2005; Janne et al., 2005; Marchetti, et al., 2005; Mitsudomi, Kosaka et al., 2005; Shigematsu et al., 2005; Tsao et al., 2005; Haneda et al., 2006].

Given this limitation, several groups have employed *EGFR* gene amplification and gene copy number to supplement or replace *EGFR* gene mutation status [Cappuzzo et al., 2005; Hirsch et al., 2005, 2006, 2007; Takano et al., 2005; Tsao et al., 2005; Han et al., 2006; Miller et al., 2008]. In a cohort of Italian patients with NSCLC, Cappuzzo and colleagues used FISH to determine gene amplification (tight gene clusters; or a ratio of *EGFR* gene-to-chromosome ≥ 2 or ≥ 15 gene copies per cell) and/or chromosome polysomy (≥ 4 chromosomes in $\geq 40\%$ of cells) [Cappuzzo et al., 2005]. In the study, 33% of cases were FISH-positive, compared to a 17% rate of *EGFR* gene mutations. FISH positivity was associated with higher radiographic response rates (36% vs 3% for FISH-negative; $P < 0.001$) and longer median survival (18.7 months vs 7.0 months for FISH-negative; $P = 0.03$). Whether *EGFR* gene mutation status or *EGFR* gene copy number is the optimal means to predict treatment outcomes remains a controversial and debated issue in NSCLC research. It appears to depend on patient population. Studies performed in predominantly Caucasian patients, in whom *EGFR* gene mutations occur rarely, tend to favor the use of *EGFR* gene copy number [Tsao et al., 2005; Cappuzzo et al., 2005]. Studies performed in East Asian countries, where *EGFR* gene mutations occur more frequently, typically favor the use of *EGFR* gene mutations [Bell et al., 2005; Takano et al., 2005; Ahn et al., 2008].

Predicting Response to anti-EGFR Monoclonal Antibodies

In contrast to their impact on EGFR TKI-based therapy, *EGFR* gene mutations do not appear to predict response to anti-EGFR mAbs [Hanna et al., 2006]. Indeed, preclinical studies of NSCLC harboring *EGFR* gene mutations have demonstrated responses to gefitinib after failure of cetuximab. This pattern has also been described in clinical case reports [Mukohara et al., 2005; Raez et al., 2005]. In general, clinical trials of cetuximab for NSCLC have required tumor specimens to be positive for EGFR by IHC. Other proposed determinants of tumor sensitivity to anti-EGFR mAbs come primarily from studies of colorectal cancer, where cetuximab has been studied more extensively. These include *EGFR* gene amplification by FISH [Moroni et al., 2005], polymorphisms in EGFR and Cyclin D1 [Zhang et al., 2006], levels of the EGFR ligands amphiregulin and heregulin [Khambata-Ford et al., 2007], mutations of the proto-oncogene *K-ras* [Khambata-Ford et al., 2007], and—reflecting the role of ADCC in the anti-tumor effect of mAbs—polymorphisms of the Fc γ receptor on host immune cells [Zhang et al., 2007].

Rash

The development and severity of an acneiform rash, the primary toxicity of EGFR inhibition, appears to correlate with disease response and survival. In studies of EGFR TKIs and anti-EGFR mAbs for multiple cancer types, including NSCLC, pancreatic, and colorectal cancers, patients who developed rash requiring clinical intervention had significantly prolonged survival compared to patients without rash [Perez-Soler et al., 2004; Jonker et al., 2007; Moore et al., 2007; Van Cutsem et al., 2007; Wacker et al., 2007; Rosell et al., 2008]. The rash arises from treatment effects on EGFR in normal epithelium. Treatment includes topical and systemic antibiotics and steroids.

CLINICAL EXPERIENCE WITH EGFR INHIBITING DRUGS FOR NSCLC

EGFR TKI Monotherapy

To date, the only form of EGFR inhibition FDA-approved for the treatment of NSCLC is second- and third-line EGFR TKI monotherapy for metastatic/recurrent disease. In May 2003, the FDA granted accelerated approval to gefitinib based on phase II clinical trials demonstrating response and survival rates comparable to those achieved with second-line cytotoxic chemotherapy [Shepherd et al., 2000; Fukuoka et al., 2003; Kris et al., 2003]. In the Iressa Dose Evaluation in Advanced Lung Cancer 1 (IDEAL 1) trial, an international study

with multiple sites in East Asia, patients with progressive, advanced lung cancer after one or two prior chemotherapy regimens were randomized to receive gefitinib 250 mg orally daily or 500 mg orally daily. For the two doses, response rate, median progression-free survival, and median overall survival were 18.4% and 19%, 2.7 months and 2.8 months, and 7.6 and 8.0 months, respectively [Fukuoka et al., 2003]. In IDEAL 2, a similarly structured study performed in the United States, radiographic responses occurred in 12% of patients receiving gefitinib 250 mg orally daily, and in 9% of patients receiving the 500-mg dose. The higher dose was not associated with higher rates of symptom improvement, radiographic tumor regression, or survival, but was associated with significantly higher rates of rash and diarrhea [Kris et al., 2003]. Accordingly, gefitinib 250 mg orally daily was the dose recommended for phase 3 studies.

The subsequent fate of gefitinib provides a lesson in the nuances of clinical trial design. The Iressa Survival Evaluation in Lung Cancer (ISEL) trial, a randomized, double-blind, placebo-controlled phase III study of gefitinib for refractory metastatic NSCLC, enrolled 1,692 patients from 210 centers in 20 countries [Thatcher et al., 2005]. Patients randomized to receive gefitinib had a significantly higher radiographic response rate compared with placebo (8% vs 1%; $P < 0.0001$), but did not have significantly longer survival (median overall survival 5.6 vs 5.1 months; $P = 0.087$). Following the negative survival result, gefitinib was relabeled for use restricted to patients already receiving and benefiting from the drug, or patients participating in clinical trials. This essentially removed the drug from the American and European markets, although it remained approved and widely used in Asia. Two phase III studies of gefitinib (one evaluating gefitinib maintenance after concomitant chemoradiation [Kelly et al., 2008]; the other evaluating adjuvant gefitinib after resection of early-stage NSCLC [NCIC BR19]) closed prematurely.

In contrast, following an encouraging single-arm phase II trial [Perez-Soler et al., 2004], a randomized, double-blind, placebo-controlled phase III clinical trial of the EGFR TKI erlotinib (NCIC BR21) demonstrated a statistically significant survival benefit, with median overall survival 6.7 months and 1-year survival 31% for patients treated with erlotinib, compared to 4.7 months and 22%, respectively, for placebo [Shepherd et al., 2005]. Erlotinib subsequently received FDA approval for second- and third-line treatment of metastatic/recurrent NSCLC. The discrepant results of the ISEL (gefitinib) and BR21 (erlotinib) trials have been attributed to differences in study populations, drug dosing and exposure, and pharmacodynamics (see Table 2) [Blackhall et al., 2006]. Specifically, eligibility criteria for ISEL required patients to have early relapsed disease—potentially selecting for a more aggressive, resistant phenotype—whereas BR21 specified no time frame for relapse. In BR21, erlotinib was administered at its maximum tolerated dose (MTD). In ISEL, the gefitinib dose was below the MTD, and the lower rates of rash and diarrhea in the ISEL trial suggest lower systemic drug exposure in this study.

EGFR TKIs Plus Chemotherapy

Because cytotoxic chemotherapy has long provided the backbone of therapy for advanced NSCLC, a number of early clinical trials of EGFR TKIs evaluated their use in combination with chemotherapy. Administering EGFR TKIs with conventional chemotherapy is biologically rational. Cellular targets and mechanisms of action differ, so cross-resistance should not arise. EGFR phosphorylation occurs in response to various cytotoxic chemotherapy drugs, rendering cells dependent on EGFR for cell survival and therefore increasingly sensitive to EGFR inhibition [Benhar et al., 2002; Azzariti et al., 2004; Sumitomo et al., 2004; Mendelsohn and Fan, 1997; Nyati et al., 2006]. EGFR TKIs may also inhibit repair of chemotherapy-induced DNA inter-strand crosslinks [Friedmann et al., 2004]. A number of

animal studies have demonstrated that EGFR TKIs potentiate the effects of cytotoxic chemotherapy [Ciardiello et al., 2000; Sirotnak et al., 2000].

Despite a compelling biologic rationale and encouraging preclinical data, four large randomized phase III trials of chemotherapy with or without an EGFR TKI in patients with advanced-stage NSCLC (altogether totaling over 4,000 patients) did not demonstrate an improvement in clinical outcomes with combination therapy (see Table 3) [Giaccone et al., 2004; Herbst et al., 2004,2005; Gandara et al., 2007]. One explanation for these results is that patients were not selected based on molecular predictors. A study population enriched for EGFR gene mutation or amplification might have benefited, but the significance of these biomarkers was not known at the time these studies were initiated. However, it must also be noted that in the pivotal phase III clinical trial of single-agent erlotinib, all categories of patients with advanced NSCLC derived survival benefit, including those otherwise expected to have low rates of biomarker positivity, such as men with extensive smoking history and squamous cell histology [Shepherd et al., 2005]. Another potential reason is that the cytostatic effect of EGFR TKIs may actually antagonize the effect of chemotherapy [Gandara and Gumerlock, 2005]. EGFR TKIs induce a G1 cell cycle arrest, which could interfere with the cell cycle-specific (S and G2/M phase) cytotoxicity of some chemotherapy drugs [Kimura, 2004; Perez-Soler et al., 2004]. This concern recalls earlier observations of tamoxifen, a hormone receptor modulator that induces G1 arrest. Breast cancer studies of adjuvant chemotherapy plus temoxifen have demonstrated superior outcomes with sequential, rather than concurrent, schedules [Albain, 2002].

To avoid the potential antagonism of EGFR TKIs and chemotherapy, more recent clinical trials of combination therapy have incorporated modified dosing schedules to achieve pharmacodynamic separation [Gandara et al., 2007]. One approach is sequential therapy, in which cytotoxic chemotherapy is administered for several cycles, then discontinued and followed by EGFR TKI therapy. A recent example is the Southwest Oncology Group (SWOG) 0023 phase III clinical trial. In this study patients with inoperable stage III NSCLC received concurrent chemoradiotherapy (cisplatin and etoposide with concurrent thoracic radiation to a total dose of 61 Gy), followed by 3 cycles of consolidation chemotherapy with docetaxel, and were then randomized to receive maintenance gefitinib 250 mg daily or placebo [Kelly et al., 2008]. Quite unexpectedly, outcomes were significantly worse among patients receiving EGFR TKI therapy. At a median follow-up of 27 months, median survival was 23 months for patients receiving gefitinib (n = 118) and 35 months for patients receiving placebo (n = 125) ($P = 0.013$). Gefitinib-associated toxicity accounted for 2% of deaths, and most patients in the gefitinib arm died due to progressive lung cancer. The investigators remarked that these results were unlikely to arise from differences in unmeasured baseline clinical (e.g., smoking status) or molecular characteristics. Instead, they postulated that chemoradiation may alter EGFR biology [Kelly et al., 2008]. Ongoing clinical trials combining chemotherapy and EGFR TKIs are incorporating intermittent dosing [Perez-Soler et al., 2004; Davies, 2005]. In these studies, EGFR TKI treatment is administered in between doses of cytotoxic chemotherapy, thereby minimizing potentially antagonistic cell cycle effects.

EGFR TKIs in Enriched Populations

To evaluate the use of EGFR TKIs for first-line NSCLC treatment, a number of phase II trials have prospectively screened patients based on molecular and clinical features to define a population most likely to benefit from such therapy (see Table 4). Response rates range from 55% to 82% and median progression-free survival ranges 8.9–13.3 months. These promising results require confirmation in randomized clinical trials, as well as a uniform means to identify the target population. If achieved, such an approach represents a rational approach to the use of targeted therapy in this disease.

Anti-EGFR mAbs

In contrast to EGFR TKIs, the anti-EGFR mAb cetuximab appears to provide the greatest benefit when combined with other treatment modalities. Cetuximab produces modest single-agent activity, with radiographic responses in fewer than 5% of patients [Hanna et al., 2006]. However, the addition of cetuximab to first-line chemotherapy, as studied previously in colorectal and head and neck cancers [Cunningham et al., 2004; Saltz et al., 2004; Burtness et al., 2005] demonstrates promising activity in NSCLC (see Table 5). In particular, the FLEX study, a randomized phase III clinical trial comparing chemotherapy (cisplatin plus vinorelbine) alone to chemotherapy plus cetuximab, has demonstrated a clinically modest though statistically significant overall survival benefit with the addition of cetuximab (OS 11.3 vs 10.1 months; HR = 0.87; 95% CI, 0.76–0.99; $P = 0.04$) [Pirker et al., 2008]. Interestingly, progression-free survival was identical in the two arms (4.8 months). In contrast to that of EGFR TKIs, the overall survival benefit was greatest in Caucasian patients ($N = 945$) (OS 11.3 vs 10.1 months; HR = 0.80 [95% CI, 0.69–0.93]; $P = 0.003$), while Asian patients ($N = 121$) had a nonsignificant trend toward worse survival with the cetuximab combination (OS 17.6 vs 20.4 months for chemotherapy alone; HR 1.18 [95% CI, 0.73–1.91]; $P = 0.49$). How these results will be incorporated into clinical practice, and whether they will lead to FDA approval of cetuximab in combination with chemotherapy for first-line treatment of NSCLC, remains to be seen.

Why might the experience with an anti-EGFR mAb plus chemotherapy seem more encouraging than that with EGFR TKIs plus chemotherapy? As shown in Table 1, mAbs provide pharmacodynamic effects beyond kinase inhibition, including EGFR degradation and long-term down-regulation, activation of ADCC, and suppression of EGFR-associated repair of DNA strand breaks [Lilenbaum, 2006; Chen and Nirodi, 2007]. EGFR TKIs are subject to the variability of oral absorption and cytochrome P-450 metabolism, whereas cetuximab is administered intravenously and has a more predictable pharmacokinetic curve. Additionally, clinical trials of cetuximab have selected patients based on positive EGFR staining in tumor samples [Gatzemeier et al.; Prenzel et al., 2001], although the degree to which EGFR expression predicts benefit from EGFR inhibitors remains controversial [Johnson and Janne, 2005].

RESISTANCE TO EGFR INHIBITION

Pathogenesis of Resistance

Although EGFR TKIs and anti-EGFR mAbs provide substantial clinical benefit to some patients with NSCLC, most NSCLC cases are resistant to EGFR inhibition. Even patients achieving dramatic responses to EGFR inhibitors, such as those whose tumors harbor *EGFR* gene mutations, generally develop resistant disease in 6–12 months [Sharma et al., 2007]. Primary or acquired resistance to EGFR inhibition may arise from specific TK domain mutations, activity of downstream signaling molecules independent of EGFR regulation, or generation of pro-survival signals through alternate molecular pathways [Camp et al., 2005; Kwak et al., 2005; Rubin and Duensing, 2006; Sequist and Lynch, 2008].

A threonine-to-methionine substitution at codon 790 in exon 20 (T790M) of the *EGFR* gene usually occurs as a secondary mutation in tumors treated with EGFR inhibitors and is thought to account for about half of all cases of acquired TKI resistance [Kosaka et al., 2004; Bell et al., 2005; Kobayashi et al., 2005; Pao et al., 2005; Inukai et al., 2006]. The bulkier methionine amino acid residue leads to a 3-dimensional change in the ATP kinase binding pocket of EGFR, resulting in steric hindrance of EGFR TKI binding [Greulich et al., 2005]. This modification of a “gatekeeper” threonine residue is structurally analogous to mutations in BCR-ABL and PGDFR conferring resistance to imatinib and other kinase inhibitors [Gorre et al., 2001; Blencke et al., 2004; Carter et al., 2005].

Activating mutations in codons 12 and 13 of the *K-ras* gene occur in 15–30% of NSCLC and appear to confer resistance to EGFR TKIs [Rodenhuis et al., 1987; Mitsudomi et al., 1991; Pao et al., 2005]. These mutations lead to constitutive activity of K-ras, a proto-oncogenic intracellular mediator downstream of EGFR (see Fig. 1), independent of EGFR signaling. *K-ras* gene mutations are strongly associated with smoking and almost always occur in the absence of *EGFR* activating mutations [Husgafvel-Pursiainen et al., 1993; Ahrendt et al., 2001; Sharma et al., 2007; Miller et al., 2008].

Molecular cross-talk and redundancy between EGFR and other signaling pathways creates alternative pathways for tumor cell proliferation, thereby bypassing EGFR and promoting resistance to EGFR inhibition (see Fig. 1). Examples include the receptor tyrosine kinases MET (which binds the ligand hepatocyte growth factor/scatter factor) [Engelman et al., 2007b; Yang et al., 2008], insulin-like growth factor receptor [Chakravarti et al., 2002; Hurbin et al., 2002], and vascular endothelial growth factor receptor (VEGFR) [Byers and Heymach, 2007; Shibuya et al., 2007; Tabernero, 2007].

Approaches to Overcoming Resistance

The two main strategies employed to overcome resistance to EGFR inhibition are the use of irreversible EGFR inhibitors and the simultaneous blocking of multiple signaling pathways with either a combination of agents or a single multi-targeted drug. In contrast to reversible first-generation EGFR TKIs, irreversible EGFR TKIs bind to EGFR covalently and appear to overcome hindrance to binding T790M mutated EGFR [Discafani et al., 1999; Smaill et al., 2000; Sharma et al., 2007]. In vitro, cancer cells that have acquired resistance to first-generation EGFR TKIs remain sensitive to irreversible EGFR inhibitors [Kwak et al., 2005].

A number of irreversible EGFR TKIs are currently in clinical trials [Erlichman et al., 2006; Sequist, 2007], as are multi-kinase targeted inhibitors. The latter include pan-ErbB (HER1, HER2, HER4) and dual EGFR/VEGFR TKIs [Engelman et al., 2007a; Heymach et al., 2007]. Clinical evidence of the activity of dual EGFR and VEGFR inhibition in NSCLC was demonstrated in a phase I/II trial of the combination of erlotinib plus the anti-VEGF mAb bevacizumab, which yielded a response rate of 20% [Herbst et al., 2005]. Among other proposed approaches are combining EGFR inhibitors with PI3K inhibitors [Ihle et al., 2005; Fan et al., 2006], mTOR inhibitors [Easton and Houghton, 2004; Doherty et al., 2006], and Ras-MAPK pathway inhibitors [Adjei, 2006].

CONCLUSIONS AND FUTURE DIRECTIONS

EGFR inhibitors have markedly changed the management of advanced NSCLC. They have introduced the concept of individualized therapy. Treatment selection may reflect patient ethnicity and gender, as well as tumor histology and molecular characteristics. EGFR inhibitors have also introduced new classes of drugs—TKIs and mAbs—to a disease previously treated with cytotoxic chemotherapy alone. These agents are generally better tolerated than traditional chemotherapy, likely improving patient quality of life. With a median age at diagnosis of 70 years, many NSCLC patients previously considered ineligible for anti-cancer therapy because of comorbidities and frailty may now receive treatment. Most importantly, EGFR inhibitors have provided proof of principle that, for the treatment of NSCLC, disease biology and treatment are inextricably linked.

Yet despite these apparent advances, for most patients with NSCLC, EGFR inhibitors have not dramatically changed clinical outcomes. The molecular complexity of lung cancer underlies these disappointments. In chronic myelogenous leukemia, almost all cases arise from a single genetic defect, a chromosomal translocation resulting in the pathognomonic BCR-ABL fusion protein. Consequently, antagonism of BCR-ABL with the TKI imatinib leads to

complete hematologic responses in almost all patients [Kantarjian et al., 2002]. In contrast, EGFR is only one of numerous aberrant biologic processes in NSCLC. Its relative importance in disease promotion and progression varies widely among patients. Ongoing research on EGFR inhibition is responding to these factors; it is hoped that it will provide incremental improvements in the outcomes of patients with this challenging disease.

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Abbreviations

ADCC, antibody-dependent cellular cytotoxicity

EGFR, epidermal growth factor receptor

FISH, fluorescence in situ hybridization

HER, human epidermal growth factor receptor

IHC, immunohistochemistry

mAb, monoclonal antibody

NSCLC, non-small cell lung cancer

PCR, polymerase chain reaction

PI3K, phosphatidylinositol-3 kinase

STAT, signal transducer and activator of transcription

TKI, tyrosine kinase inhibitor

VEGFR, vascular endothelial growth factor receptor.

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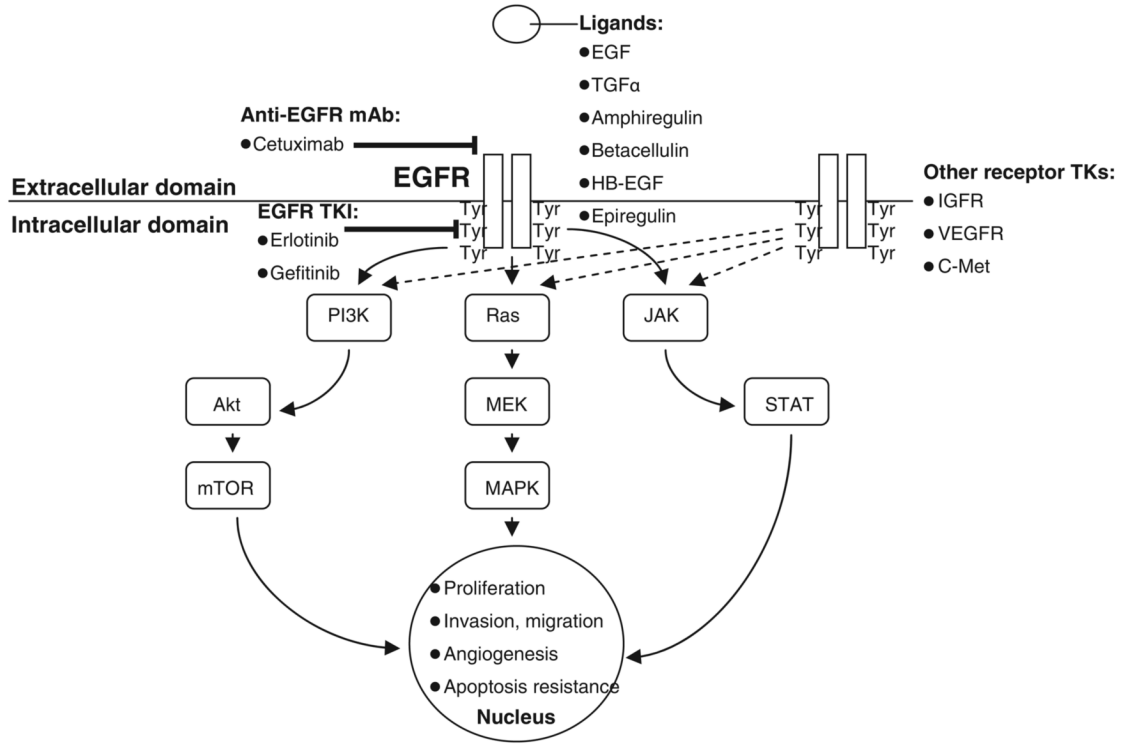


Fig. 1. EGFR signaling, actions, and inhibition in NSCLC. Dashed lines indicate redundant molecular signaling pathways potentially causing resistance to EGFR inhibition. Abbreviations: EGF, epidermal growth factor; HB-EGF, heparin-bound EGF; IGFR, insulin-like growth factor receptor; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal-regulated kinase kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3 kinase; STAT, signal transducer and activator of transcription; TGF- α , transforming growth factor- α ; TK, tyrosine kinase; TKI, tyrosine kinase inhibitor; Tyr, tyrosine; VEGFR, vascular endothelial growth factor receptor.

TABLE 1

Features of EGFR-Inhibiting Drugs for the Treatment of NSCLC: Tyrosine Kinase Inhibitors (TKIs) and Monoclonal Antibodies (mAbs)

	Tyrosine kinase inhibitors (TKIs)	Monoclonal antibodies (mAbs)
Examples in NSCLC	Erlotinib (Tarceva) Gefitinib (Iressa)	Cetuximab (Erbiximab)
Site of action	Intracellular	Extracellular
Mechanism(s)	Inhibition of tyrosine kinase function	Antagonism of ligand-receptor binding; internalization Internalization, degradation of EGFR; recruitment of host immune functions (e.g., ADCC)
Molecular weight	400–500 daltons	150,000 daltons
Administration	Oral	Intravenous
Hypersensitivity reactions	None	Yes
Half-life	1–2 days	5 days
Drug interactions	Multiple (CYP450 substrate)	Minimal

ADCC, antibody-dependent cellular cytotoxicity; CYP-450, cyto-chrome P-450; NSCLC, non small cell lung cancer; EGFR, epidermal growth factor receptor.

TABLE 2

Comparison of Phase III Clinical Trials of Single-Agent EGFR TKI Therapy in Recurrent/Refractory Advanced NSCLC

	Gefitinib	Erlotinib
Phase III clinical trial	ISEL (Iressa Survival Evaluation in Lung Cancer)	NCIC BR21
Study population	<i>Early</i> relapse/progression (within 90 days) after prior platinum chemotherapy	Relapse/progression (no time limit specified) after prior platinum chemotherapy
Affinity for EGFR (IC ₅₀)	5 nmol/L	2 mnol/L
Maximum tolerated dose	700mg	150mg
Dose selected for trial	250mg	150mg
Frequency of rash	37%	76%
Frequency of diarrhea	27%	55%

Data from Blackhall et al. [2006] and Sharma et al. [2007].

TABLE 3
Phase III Clinical Trials of EGFR TKIs Plus Chemotherapy in First-Line NSCLC Treatment

Study	Treatment	RR (%)	TTP (mo)	OS (mo)	P	Reference
INTACT-1	Gemcitabine/Cisplatin	47.2	6	10.9	NS	Giaccone et al., 2004
	Gemcitabine/Cisplatin + Gefitinib 250	51.2	5.8	9.9		
	Gemcitabine/Cisplatin + Gefitinib 500	50.3	5.5	9.9		
INTACT-2	Carboplatin/Paclitaxel	28.7	5	9.9	NS	Herbst et al., 2004
	Carboplatin/Paclitaxel + Gefitinib 250	30.4	5.3	9.8		
TALENT	Carboplatin/Paclitaxel + Gefitinib 500	30	4.6	8.7		
	Gemcitabine/Cisplatin	28.2	5.6	10.1	NS	Gatzemeier et al., 2007
	Gemcitabine/Cisplatin + Erlotinib 150	30	5.4	9.9		
TRIBUTE	Carboplatin/Paclitaxel	19.3	4.9	10.6	NS	Herbst et al., 2005
	Carboplatin/Paclitaxel + Erlotinib 150	21.5	5.1	10.8		

NS, not significant; OS, overall survival; RR, response rate; TTP, time to progression.

TABLE 4
Clinical Trials of First-Line, Single-Agent EGFR TKI Therapy in Enriched Patient Populations With NSCLC

Study	Selection criteria	Treatment	RR (%)	PFS (mos)	Reference
Paz-Ares et al.	Classic (Exon 19 or 21) <i>EGFR</i> gene mutation	Erlotinib	82	13.3	Paz-Ares et al., 2006
Asahina et al.	Classic <i>EGFR</i> gene mutation	Gefitinib	75	8.9	Asahina et al., 2006
Inoue et al.	Classic <i>EGFR</i> gene mutation	Gefitinib	75	9.7	Inoue et al., 2006
iTARGET	Any <i>EGFR</i> gene mutation	Gefitinib	55	11.4	Sequist et al., 2008

PFS, progression-free survival; RR, response rate.

TABLE 5
Clinical Trials of anti-EGFR mAbs Plus Chemotherapy in First-Line NSCLC Treatment*

Study	Design	Treatment	RR (%)	PFS (mo)	OS (mo)	Reference
Thienelt et al.	Phase II	Carboplatin/Paclitaxel + Cetuximab	26	5	11	Thienelt et al., 2005
Robert et al.	Phase II	Carboplatin/Gemcitabine + Cetuximab	28	5.3	10.3	Robert et al., 2005
Rosell et al.	Rand. phase II	Cisplatin/Vinorelbine + Cetuximab vs Cisplatin/Vinorelbine	35 28	4.8 4.3	8.3 7	Rosell et al., 2008
Kelly et al.	Rand. phase II	Concurrent Carboplatin/Paclitaxel + Cetuximab vs Sequential Carboplatin/Paclitaxel + Cetuximab	37 26	4.2 4.4	10.5 8.7	Kelly et al., 2008
Butts et al.	Rand. phase II	Platinum ^a /Gemcitabine + Cetuximab vs Platinum ^a /Gemcitabine	28 18	5.1 4.2	12.0 9.3	Butts et al., 2007
BMS 099	Rand. phase III	Carboplatin/Taxane ^b + Cetuximab vs Carboplatin/Taxane ^b	26 17	4.4 4.2	NR NR	Lynch, 2007
FLEX	Rand. phase III	Cisplatin/Vinorelbine + Cetuximab vs Cisplatin/Vinorelbine	36 29	4.8 4.8	11.3 10.1	Pirker et al., 2008

IHC immunohistochemistry; OS, overall survival; PFS, progression-free survival; RR, response rate; EGFR, epidermal growth factor receptor.

* In all studies except BMS 099, patients were required to have tumors with EGFR expression.

^a Choice of platinum (cisplatin or carboplatin) determined by investigator before randomization.

^b Choice of taxane (paclitaxel or docetaxel) determined by investigator before randomization.