Erlotinib in cancer treatment

M. A. Bareshino, C. Schettino, T. Troiani, E. Martinelli, F. Morgillo & F. Ciardiello*

Division of Medical Oncology, Department of Clinical and Experimental Medicine and Surgery “F. Magrassi and A. Lanzara”, Second University of Naples, School of Medicine, Naples, Italy

The epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase (TK) receptor that is frequently expressed in many epithelial tumors. The signaling pathways of EGFR is involved in cancer cell proliferation, apoptosis, angiogenesis, invasions and metastasis. The EGFR was the first receptor to be proposed for cancer therapy and two EGFR-targeted pharmacological approaches have been successfully developed: monoclonal antibodies and small-molecule inhibitor of the EGFR TK enzymatic activity. Erlotinib is a quinazoline derivative that selectively and reversibly inhibits the TK activity of EGFR. Erlotinib, on the basis of the results of a large randomized phase III clinical trial (BR21) in which show a survival benefit versus placebo-treated patients, received regular approval for the treatment of advanced non-small-cell lung cancer (NSCLC) patients after failure a platinum-containing chemotherapy. Erlotinib was recently approved in combination with gemcitabine chemotherapy for the treatment of advanced pancreatic cancer, and continues to be investigated in a number of tumor types. Furthermore, it has been investigated the role of factors that would predict the efficacy of erlotinib treatment, including anatomicclinical, pathologic and molecular features. This review will focus on the clinical results available with erlotinib in the treatment of NSCLC, pancreatic, head and neck and other tumor types.

Key words: EGFR pathways, erlotinib, NSCLC, pancreatic cancer

introduction

The epidermal growth factor receptor (EGFR) is a member of the ErbB family cell membrane receptors that are important mediators of cell growth, differentiation and survival. The ErbB family also includes ErbB-2/Neu/HER2, ErbB-3/HER3 and ErbB-4/HER4. The EGFR (also known as ErbB-1/HER1) is a 170-kDa transmembrane glycoprotein that consists of an extracellular domain that recognizes and binds to specific ligands, a hydrophobic transmembrane domain, involved in interactions between receptors within the cell membrane, and an intracellular domain that contains the tyrosine kinase (TK) enzymatic activity. The epidermal growth factor (EGF) belongs to a family of related peptides (EGF-like growth factor), which include transforming growth factor α (TGFα), amphiregulin, heparin binding-EGF, epiregulin, heregulin, neuregulins [1, 2] and betacellulin [1]. EGFR-like growth factors bind to activate one or more receptor of the ErbB family. Once the ligand binds to the extracellular domain, EGFR undergoes homodimerization or heterodimerization. Dimerization induces the activation of the TK domain which leads to autophosphorylation of critical tyrosine residues on the cytoplasmic terminal. These tyrosine residues serve as attachment sites for a range of cellular-docking proteins, activating a variety of downstream signaling cascades to affect gene transcription [3]. Three pathways downstream of EGFR have been identified: the Ras/Raf mitogen-activated protein kinase, Phosphoinositide-3 kinase (PI3K)/Akt and Jak2/STAT3 pathways. Activation of these pathways starts a cascade of complex cell biochemistry that regulates cell proliferation, inhibition of programmed cell death (apoptosis), angiogenesis, invasion and metastasis. The EGFR is frequently expressed in a variety of epithelial tumors; non-small-cell lung cancer (NSCLC) is among the epithelial cancers that are characterized by a generally high expression of ligands and receptors belonging to the EGFR system [1] with an expression of ~40%–80%. EGFR overexpression has also been demonstrated in colorectal cancer (72%–82%), head and neck cancer (95%–100%), breast cancer (14%–91%) and renal cell cancer (50%–90%) [4]. The blockade of EGFR signaling in cancer cells inhibits not only cell proliferation but also other effects that could be relevant in the clinical setting including induction of apoptosis, anti-angiogenesis through inhibition of angiogenic growth factor production, inhibition of invasion and metastasis and potentiation of antitumor activity of cytotoxic drugs and of radiotherapy [1].

Two EGFR-targeted pharmacologic approaches have resulted in clinical activity in cancer patients: monoclonal antibodies (mAbs), such as cetuximab and panitumumab, raised against the extracellular domain of EGFR to block ligand binding and receptor activation and small-molecule inhibitors of EGFR tyrosine kinase, such as gefitinib and erlotinib, that prevent EGFR autophosphorylation and downstream signaling. This review focuses on the clinical...
development and future prospective of erlotinib in cancer treatment.

erlotinib

Erlotinib (Tarceva®, OSI-774; Genetech Roche, Basel, Switzerland) is an oral low-molecular weight quinazoline-based agent that selectively and reversibly inhibits the TK activity of EGFR competing with adenosine triphosphate for binding in the receptor’s TK domain [5].

Erlotinib is ~60% absorbed after oral administration. Once absorbed, erlotinib is 93% protein bound. Erlotinib is metabolized through the cytochrome P450 system primarily by CYP3A4. The drug is mainly excreted in feces with a half-life of ~36 h. The maximal tolerated dose of erlotinib on a protracted daily schedule was 150 mg/daily. The dose-limiting toxic effects were diarrhea and skin rash [6]. The antitumor activity of erlotinib as single-agent therapy has been observed in heavily pretreated patients with advanced head and neck cancer, ovarian cancer and NSCLC [7–9].

Erlotinib has been approved by the Food and Drug Administration (FDA) (USA) in November 2004 and by the European Medicinal Evaluation Agency (EU) in October 2005 for the treatment of chemotherapy-resistant advanced NSCLC patients, and in November 2005 by FDA in combination with gemcitabine chemotherapy for the treatment of advanced pancreatic cancer in patients who have not received previous chemotherapy.

erlotinib in NSCLC

Erlotinib treatment as a single agent has been evaluated in advanced NSCLC patients after failure of one or two standard chemotherapy regimens in a large (731 patients), multicenter randomized phase III clinical trial (BR21 study) in comparison with best supportive care[10]. These patients had a metastatic NSCLC, which was treated with one standard chemotherapy regimen (50% of patients) or with two chemotherapy regimens (50% of patients). Almost all patients received a platinum-based therapy. The response rate (RR) was 8.9% in the erlotinib arm and <1% in the placebo group (P < 0.001). The median duration of response was 7.9 and 3.7 months, respectively. Overall survival (OS) was 6.7 months for those in the erlotinib regimen compared with 4.7 months in the placebo arm [P < 0.001, hazard ratio (HR) = 0.7]. Progression-free survival (PFS) was 2.2 months with erlotinib and 1.8 months with placebo (P < 0.001, HR = 0.70). Five percent of patients discontinued erlotinib due to toxicity. This study showed that erlotinib significantly prolonged survival and improved symptoms. Objective responses were more frequent in women (14% versus 6%, P = 0.0065), in patients with adenocarcinoma as compared with other histotypes (14% versus 4.1%, P < 0.0001) and in patients without smoking history (25% versus 4%, P < 0.0001). Quality of life (QoL) evaluation, defined as the time to clinically significant deterioration in three common lung cancer symptoms, showed that patients receiving erlotinib had significantly longer median time to deterioration for all three symptoms [4.9 versus 3.7 months for cough (P = 0.04), 4.7 versus 2.9 months for dyspnea (P = 0.04) and 2.8 versus 1.9 months for pain (P = 0.03)]. QoL response analyses showed that 44%, 34% and 42% of patients receiving erlotinib had improvement in these three symptoms, respectively. This was accompanied by a significant improvement in the physical function (31% erlotinib versus 19% placebo, P = 0.01) and global QoL (35% versus 26%, P < 0.0001) [11] (Table 1).

Erlotinib as single agent has been also tested as first-line treatment in advanced NSCLC patients [15]. Fifty-three chemotherapy-naive patients with stage IIIb/IV NSCLC received oral erlotinib (150 mg/day) until disease progression or unacceptable toxicity occurred. The overall rate of progression-free survival was 36% for patients treated with erlotinib in comparison with 9% in the placebo group (P = 0.0001). The median duration of response was 7.9 versus 6.3 months for those in the erlotinib arm and 4.7 versus 3.7 months for those in the placebo arm (P = 0.03). QoL response analyses showed that 44%, 34% and 42% of patients receiving erlotinib had improvement in these three symptoms, respectively. This was accompanied by a significant improvement in the physical function (31% erlotinib versus 19% placebo, P = 0.01) and global QoL (35% versus 26%, P < 0.0001) [11] (Table 1).

Table 1. Phase III randomized trials with erlotinib in advanced non-small cell lung cancer and pancreatic cancer

<table>
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<tr>
<th>Trial design</th>
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<td>GEM versus GEM + erlotinib, NCIC-CTG trial [14]</td>
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CBDCA, carboplatin; CDDP, cisplatin; EGFR, epidermal growth factor receptor; GEM, gemcitabine; NSCLC, non-small-cell lung cancer; PTX, paclitaxel; TTP, time to progression.
nonprogresion at 6 weeks was 52.8% (28 of 53 patients). Tumor RR was 22.7%, with 1 complete response (CR), 11 partial response (PR), and 16 cases of stable disease (SD). The median duration of tumor response was 333 days, median OS was 391 days and median time to disease progression was 84 days.

Recently, erlotinib has been tested in a phase II study in patients aged >70 years with previously untreated advanced NSCLC. The 51% disease control rate (PR + SD) in this trial is very similar to the rate found in the BR21 trial (45%). The median time to progression (TTP) was 3.5 months, whereas median survival was 10.9 months. The 1- and 2-year survival rates were 46% and 19%, respectively. The toxicity of erlotinib in this population compares favorably with other studies carried out in patients with NSCLC older than 70 years of age. The relative tolerability of erlotinib in these patients' population may represent an important first-line option [16].

Two phase III randomized, double-blind placebo-controlled trials assessed erlotinib with combination chemotherapy in the first-line setting: the TRIBUTE trial [erlotinib with paclitaxel (Taxol) and carboplatin] and the TALENT trial (erlotinib with cisplatin and gemcitabine) (Table 1).

In the TRIBUTE trial, there was no difference found in patients treated with erlotinib and carboplatin/paclitaxel in comparison with those treated with carboplatin/paclitaxel alone: OS was 10.8 months with erlotinib versus 10.6 months with placebo (HR 0.95, 95% confidence interval [CI] 0.8–0.85) [12]. Also in the TALENT trial, there was no statistically significant difference in OS (301 versus 309 days, respectively), TTP (167 versus 179 days, respectively) and QoL between patients treated with erlotinib or placebo. Therefore, there was no clinical benefit in either trial, and currently concurrent use of erlotinib with chemotherapy in NSCLC is not recommended in the first-line treatment of NSCLC [13].

On the basis of the rationale dual blockade of the EGFR signaling pathway and vascular epithelial growth factor (VEGF), that may produce additive and synergistic cytostatic effects, non-squamous stage IIIB/IV NSCLC patients pretreated with one or more prior chemotherapy were enrolled in a phase I/II trial that examined erlotinib and bevacizumab combined treatment. A total of 40 patients were enrolled, 34 were treated at the phase II dosages and for these, RR was 20%, the median survival time (MST) 12.6 months and the PFS 6.2 months [17].

Since the first reports on the activity of anti-EGFR small-molecule tyrosine kinase inhibitors (TKIs) in NSCLC, a series of clinical and biological characteristics of potential predictiveness of response have been indicated. The clinical markers that are more often been associated with a response to treatment with erlotinib are female sex, Asian ethnicity, never smokers and adenocarcinoma histology. In the BR21 study, erlotinib had a significant effect on survival in all subgroup of patients [10]. In fact, even if male smokers with squamous cell carcinoma have not been considered ideal candidates for treatment with erlotinib, in this group MST was significantly improved among patients receiving erlotinib (n = 100) compared with patients with similar characteristics in the placebo arm (n = 57) (HR = 0.66, 95% CI 0.47–0.92, P = 0.016).

This difference resulted in MST of 5.5 months in the erlotinib arm compared with 3.4 months in the placebo arm [18]. The effect of smoking was also examined in the TRIBUTE phase III trial. Despite a lack of benefit in the overall patient population, when the analysis was confined to those who had never smoked cigarettes, erlotinib seemed to confer a survival benefit (MST of 10 and 22.5 months for smokers and never smokers, respectively; P = 0.01) [12].

Among molecular predictors, EGFR gene somatic mutation is the first molecular marker that could be clinically useful to select NSCLC patients. The more common mutations are an in-frame deletion in exon 19 around codons 746–750 and a missense mutation leading to leucine to arginine substitution at codon 858 (L858R) in exon 21 [19]. The association of sensitivity to erlotinib with EGFR gene mutations has been on the basis of retrospective data mostly collected from patients treated on BR21 and TRIBUTE trials. In the TRIBUTE trial, EGFR mutations were found in 13% of cases and were correlated with an increased RR to erlotinib plus chemotherapy (53%) compared with EGFR wild-type cases (18%). Patients with EGFR mutations also showed an increased response to either treatment (38%) compared with wild-type cases (23%, P = 0.01), and a prolonged survival, which was independent of treatment (8 versus 5 months for mutation-positive and -negative groups, respectively; P < 0.001) [20], whereas retrospective analysis of the BR21 trial failed to prove this association [21].

Another interesting aspect that emerged from retrospective analysis of clinical trials is the role of EGFR gene amplification. In the BR21 trial, FISH-positive patients (~40%) randomized to receive erlotinib had a significantly superior survival (HR = 0.44, P = 0.01), as compared with FISH-negative patients randomized into the placebo arm (HR = 0.44, P = 0.01). In the FISH-negative patients, there were no significant differences in survival. Interestingly, a significant correlation between the high presence of EGFR gene copy number and mutations was seen [22, 23], indicating that the mutant allele of the EGFR gene is selectively amplified in tumors, as it has been observed in EGFR-mutant NSCLC cell lines.

Also the high levels of EGFR protein expression, as determined by immunohistochemistry (IHC), appear associated with response and survival in a retrospective subset analysis of the BR21, in which IHC-positive patients treated with erlotinib had a significantly superior survival compared with placebo-treated patients (HR 0.68, P = 0.02) [21].

Molecular characterization of EGFR gene abnormalities in NSCLC has provided a fascinating window into the future of genotype-directed targeted therapy for a common epithelial cancer.

**erlotinib in pancreatic cancer**

Pancreatic cancer persists as a major therapeutic challenge largely characterized by chemotherapy-refractory disease and poor responses to currently available treatments. The EGFR is
overexpressed in pancreatic cancer and there are data to indicate that this molecular characteristic may be a poor prognostic factor as it may denote a more aggressive form of the disease.

The combination of gemcitabine and erlotinib as first-line treatment for pancreatic cancer was assessed in a multicenter, phase III randomized, double-blind placebo-controlled trial. In this study, 569 patients with advanced pancreatic cancer were randomized to receive gemcitabine 1000 mg/m²/week for 7 of 8 weeks and then for 3 of every 4 weeks plus either erlotinib 100 mg per day or a placebo. The addition of erlotinib to gemcitabine was associated with a small but significant improvement of 1-year OS (24% versus 17%, HR = 0.81, P = 0.028) and median survival (6.4 months versus 5.9 months) when compared with gemcitabine alone. Interestingly, while the overall RR was significantly higher in the arm receiving erlotinib (58% versus 49%, P = 0.036), this was primarily due to an increase in SD with no significant difference in PR. A significant improvement in PFS (HR = 0.76, P = 0.006) also was demonstrated. QoL analysis revealed similar results for both groups [14] (Table 1).

Erlotinib is also being evaluated in combination with capecitabine, in phase II trial, for patients with metastatic pancreatic cancer who have already failed first line therapy with gemcitabine. The regimen was generally well tolerated with 14% of patients experiencing grades 3 and 4 rash and diarrhea. Eleven percent of patients have achieved PR and 57% have achieved SD with median survival of 6.7 months, all of which are fairly encouraging for pancreatic cancer salvage therapy [24].

A preliminary analysis of one phase II study randomizing patients with advanced pancreatic cancer to gemcitabine and bevacizumab with either cetuximab (gemcitabine bevacizumab cetuximab [GBC]) or erlotinib (gemcitabine bevacizumab erlotinib [GBE]) was presented at the most recent Annual Meeting of the American Society of Clinical Oncology in Atlanta. Both arms have demonstrated significant activity with RR of 19% and 21%, respectively, and SD rate of 59% and 67%, respectively. Both regimens have been fairly well tolerated thus far with the bulk of the toxic effects ascribed to bevacizumab [25].

Several phase I studies have also been carried out to assess the feasibility of TKIs in combination with radiotherapy. One of these trials analyzed a novel regimen of concomitant gemcitabine, paclitaxel and erlotinib concurrent with radiotherapy followed by maintenance of erlotinib until disease progression. The maximally tolerated dose of erlotinib during the radiotherapy phase was 50 mg. There were multiple dose-limiting toxic effects described including diarrhea, rash, myelosuppression and small bowel stricture, but results were encouraging with a reported 46% rate of PR [26].

**erlotinib in head and neck cancer**

Targeting EGFR as a therapeutic strategy against head and neck squamous cell cancer (HNSCC) is a rational approach substantiated by multiple lines of evidence. The overexpression of EGFR in 80%–100% of HNSCCs corroborates the potential clinical relevance of this target. Furthermore, elevated levels of EGFR and TGFβ messenger RNA have been detected in tumors and in histologically normal mucosa from patients with HNSCC, when compared with control normal mucosa [27]. Importantly, several reports have provided support for a clinicopathologic association between EGFR overexpression and poorer prognosis, such as decreased chemosensitivity and shorter disease-free survival for patients with HNSCC [28, 29].

A multicenter phase II study has been conducted to determine the efficacy and safety profile of erlotinib administered as a single agent in patients with refractory recurrent and/or metastatic HNSCC. One hundred fifteen patients were enrolled on to this study. Forty-seven percent of patients received erlotinib at 150 mg daily throughout the entire study, 6% had dose escalations and 40% required dose reductions and/or interruptions. Five patients achieved PR on study for an overall objective RR of 4.3% (95% CI 1.4% to 9.9%). Disease stabilization was maintained in 44 patients (38.3%) for a median duration of 16.1 weeks. The median PFS was 9.6 weeks (95% CI 8.1–12.1 weeks), and the median OS was 6.0 months (95% CI 4.8–7.0 months). Subgroup analyses revealed a significant difference in OS-favoring patients who developed at least grade 2 skin rashes versus those who did not (P = 0.045), whereas no difference was detected on the basis of EGFR expression [7].

The combination of erlotinib and cisplatin in patients with recurrent or metastatic HNSCC has been evaluated in a phase II clinical trial. Among 31 patients of the 35 enrolled, seven objective responses have been observed (1 CR, 6 PR [1 unconfirmed], 12 SD and 6 PD) in 25 assessable patients. This schedule of erlotinib plus cisplatin has antitumor activity comparable to standard cisplatin-based combination chemotherapy regimens and may have a more favorable toxicity profile [30].

On the basis of the synergy and efficacy of platinum and taxanes [31] combination in HNSCC, a phase II trial has evaluated the addition of erlotinib to cisplatin–docetaxel doublet. Thirty-seven patients have been enrolled thus far. Three CR, 18 PR and 8 SD for an overall RR of 66% and disease control rate of 91% have been observed. These preliminary data indicate that the combination of cisplatin, docetaxel and erlotinib is well tolerated and has very encouraging early activity in advanced HNSCC [32].

The role of erlotinib in neo-adjuvant setting in HNSCC patients and the opportunity to find predictive factors of response have been evaluated in a pilot clinical trial. In this study, 35 patients were recruited, among 30 evaluated patients, 8 were considered as good responders (30%–80% decrease in tumor size), 18 had SD and 2 had minor progression. The treatment was well tolerated, and did not modify the routine surgical procedure. Neither overexpression of EGFR nor other IHC markers alone were found to be good predictive markers of efficacy. Retrospective analysis of morphological and IHC evaluation in same cell cycle regulators (p21) appeared to be predictive of erlotinib efficacy [33].

**erlotinib in other solid tumors**

Encouraging indications of antitumor activity were also reported in several phase II studies outside of NSCLC.
including monotherapy use of erlotinib in colorectal, hepatocellular, biliary, gastroesophageal, and ovarian cancer.

The efficacy and safety of single-agent erlotinib has been tested in advanced gastroesophageal junction (GEJ) and gastric adenocarcinoma cancer, in a phase II trial (SWOG 0127). In this multicentre trial, 43 patients with cancer of the GEJ and 25 with gastric cancer received 150 mg/day oral erlotinib for 4 weeks per cycle. In the GEJ stratum, there was one CR, three confirmed PR, with an objective RR of 9% (95% CI 3% to 22%). There were no objective responses in the gastric arm. Median survival was 6.7 months for those with GEJ tumors and 3.5 months for those with gastric cancer, and median time to treatment failure was 2 and 1.6 months, respectively. In conclusion, erlotinib is active in patients with GEJ cancer, but appears inactive in gastric cancer. The molecular correlates examined, in this trial, were not predictive of the patients’ therapeutic response [34].

A variety of approaches are being investigated to improve ovarian cancer outcome such as EGFR inhibitors. EGFR is also overexpressed in a significant percentage of epithelial ovarian cancer (35%–70%) and has been associated with poor prognosis [35]. The efficacy and safety of erlotinib in patients with refractory, recurrent EGFR-positive epithelial ovarian cancer was evaluated in a multicenter phase II study. Among 34 patients enrolled, two patients had PR (RR of 6%; 95% CI 0.7% to 19.7%). Fifteen patients (44%) had SD, and 17 patients (50%) had PD. Median OS was 8 months (95% CI 5.7–12.7 months), with a 1-year survival rate of 35.3% (95% CI 19.8% to 53.5%). Patients with rash survived significantly longer than those without (P = 0.009), correlating with rash grade. Erlotinib had marginal activity but was generally well tolerated. The safety profile appears more favorable than typically experienced with standard chemotherapeutic agents, which is encouraging in these heavily pretreated patients [8].

EGFR represents a particularly attractive target in malignant gliomas because the receptor is expressed, amplified or mutated in most cases [36]. Moreover, because intracranial delivery of many agents is limited, small-molecule TKIs offer a pharmacologic advantage for brain malignancies. Erlotinib has shown activity in recurrent glioblastoma multiforme (GBM) in a phase II clinical trial with a promising RR 8.4% (three PR, one CR), with SD as the best response in 37.5%; 6 months PFS was 17% and median survival 10 months in a cohort of 48 patients. Molecular analysis shows a slight trend toward better outcome with EGFR expression; however, the differences are not significant due to the small numbers [37]. Similar results were observed in other phase II trial of erlotinib single-agent therapy in recurrent GBM [38].

In colorectal cancer, single-agent treatment with TKIs (erlotinib, gefitinib) seems to be able to achieve disease stabilization in ~30% of patients, whereas objective responses were only reported in a single phase II trial in which has been tested erlotinib in chemorefractory metastatic colorectal cancer (mCRC) patients. In this trial, 41 patients were treated with erlotinib after either one (cohort 1) or two (cohort 2) prior 5-fluorouracil-based chemotherapy. Among 24 patients evaluated were reported 8% PR (two patients), 33% SD, resulting in a disease of control rate 41% [39]. Furthermore, the combination of erlotinib-targeted therapy against the VEGF receptor (bevacizumab) and cytotoxic chemotherapy appears to have a moderate toxicity profile in untreated mCRC patients [40].

Studies have indicated that EGFR is actively expressed in human hepatocytes, that EGF may be one of the mitogens needed for the growth of hepatocytes cell lines [41] and its role might be more important in poorly differentiated hepatocytes cells than in the well-differentiated ones [42]. The lack of any clinically useful drug therapy for patients with advanced hepatocellular cancer (HCC) and the hypothesis that using EGFR blockade could reduce the growth of these tumors and delay the progression of the disease represent the rational of a phase II clinical trial in which 38 advanced or metastatic HCC patients were treated with erlotinib. Results of this trial revealed activity of erlotinib as single agent in treating patients with advanced HCC that was similar to that seen with EGFR blockade in other EGFR-expressing tumor types [43]. Twelve (32%; 95% CI 18–49) of the 38 patients with HCC were progression-free at 6 months. Three patients had partial radiologic responses of duration of 2, 10 and 11 months, respectively. Disease control was seen in 59% of the patients and median OS time was 13 months [44].

Finally, recently erlotinib has been evaluated in the treatment of advanced biliary cancer patients in a phase II clinical trial that has demonstrated a modest activity in this population of patients [45].

**conclusions**

In the last years, the EGFR has emerged as one of the most important target for drug development in oncology. mAbs targeting the external domain of EGFR have been shown to have clinical benefit in colorectal and head and neck cancer when combined with chemotherapy and/or radiation. Small molecules that inhibit the TK domain of EGFR have become critical new weapons above all in the treatment of NSCLC. Erlotinib not only has shown promising clinical activity as monotherapy in a small subset of chemotherapy-refractory NSCLC patients, but also has been shown to significantly improve survival in an unselected population of patients following the failure of one or two chemotherapy regimens. Moreover, erlotinib has been shown to add a survival benefit when combined with gemcitabine for patients with pancreatic cancer. Of note, erlotinib has also activity in head and neck tumors, in glioblastoma and in other tumor types. Since the initial clinical trials in NSCLC has been investigated the role of clinical factors, pathologic and molecular features that would predict the efficacy of erlotinib. Although further research is necessary, new paradigms for clinical decision-making may emerge by identifying EGFR gene alterations and alteration in gene-coding downstream proteins such as K-ras.

Finally, the majority of EGFR-expressing tumors have a complex genetic background and there is a significant level of compensatory ‘cross talk’ among receptors within a signaling network as well as with other pathways regulating cell proliferation, trafficking and survival. As with conventional chemotherapeutic agents, rationally developed biologically and molecularly targeted combinations are going to be likely to
enhance the contribution of these agents to the treatment of
cancer.

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