Current and Emerging Roles of Epidermal Growth Factor Receptor Inhibitors in Advanced Non-Small Cell Lung Cancer

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Abstract: Recent advances in basic and translational research have elucidated important molecular alterations that underlie neoplastic transformation and progression in non-small cell lung cancer (NSCLC). Specifically, the epidermal growth factor receptor (EGFR) signal transduction pathway presents therapeutic opportunities at various levels from the extracellular ligands to the transmembrane receptor and associated intracellular tyrosine kinase and the downstream signaling molecules. Two main categories of molecular agents targeting the EGFR-associated network have been incorporated into clinical practice: monoclonal antibodies that interfere with the binding of the natural ligand to the receptor (e.g. cetuximab) or tyrosine kinase inhibitors (e.g. erlotinib, gefitinib) that inhibit the activation of receptor tyrosine kinase leading to abrogation of signal propagation. Several other EGFR-targeting agents are currently under intensive preclinical and clinical investigation. In the current review we summarize data concerning the current and emerging role of EGFR-targeting molecules in the treatment of NSCLC.

Keywords: Non-small cell lung cancer, EGFR, monoclonal antibodies, tyrosine kinase inhibitors.

1. INTRODUCTION

Lung cancer remains the most lethal human malignancy, accounting for an estimated 1.1 million deaths annually worldwide [1]. Histologically, almost all types of lung cancer are of epithelial origin and include two main subtypes: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which account for 15% and 85% of all cases diagnosed in the United States annually, respectively [2]. Despite incremental improvements in lung cancer therapeutics, overall prognosis remains dismal, with 5-year survival rates including all stages of disease of about 15% in the United States [3]. Adenocarcinoma is the most frequent histologic subtype of NSCLC and the predominant diagnosis among never-smokers [3, 4].

Recent advances in molecular biology provided insights into the role of proliferative signals in the acquisition of a malignant phenotype by the respiratory epithelial cell. This signaling cascade can be segregated into three distinct but interlocking phases (Fig. **1**). The upstream phase consists of the interaction of growth factors or ligands and the associated membrane receptors through the complimentary extracellular binding domain. This leads to receptor homo- or heterodimerization and subsequent conformational changes that trigger the activation of the protein kinase activity located in the intracellular domain. These enzymes catalyze the covalent attachment of phosphate groups to amino acid residues (serine, threonine or tyrosine) of cytoplasmic proteins with resultant activation or inactivation, thus facilitating the transduction of the signal from the cell membrane to the nucleus [5]. The epidermal growth factor (EGF) signaling cascade is a prototype ligand-activated signaling network whose key components can be deregulated through various mechanisms leading to enhancement of cellular proliferation, disordered apoptosis and increased cellular invasiveness and metastasis [6]. Different components of the EGF pathway constitute potential therapeutic targets for novel anticancer therapies. In the current review we focus on the established and emerging roles of agents targeting the EGF receptor (EGFR) and its receptor-associated tyrosine kinase (TK) activity in NSCLC.

2. EPIDERMAL GROWTH FACTOR RECEPTOR IN NSCLC

EGFR (ERBB1) is a member of the family of tyrosine kinase receptors called ERBB, comprising also ERBB2 (HER2/neu), ERBB3 (HER3) and ERBB4 (HER4). EGFR is a transmembrane glycoprotein that consists of an intracellular domain possessing TK activity, a transmembrane lipophilic domain and an extracellular portion that is responsible for the binding of the ligands (e.g. EGF) (Fig. **1**). EGFR is encoded by a gene located on the short arm of chromosome 7 and specifically in the 7p12.1-12.3 region consisting of 26 exons. Exons 1-14 code for the extracellular portion, exon 15 for the transmembrane and exons 16-20 for the intracellular domains of the receptor [7].

EGFR is expressed in a number of solid tumors, including colorectal cancer, head and neck cancer and lung cancer [8]. EGFR and HER2 are overexpressed in

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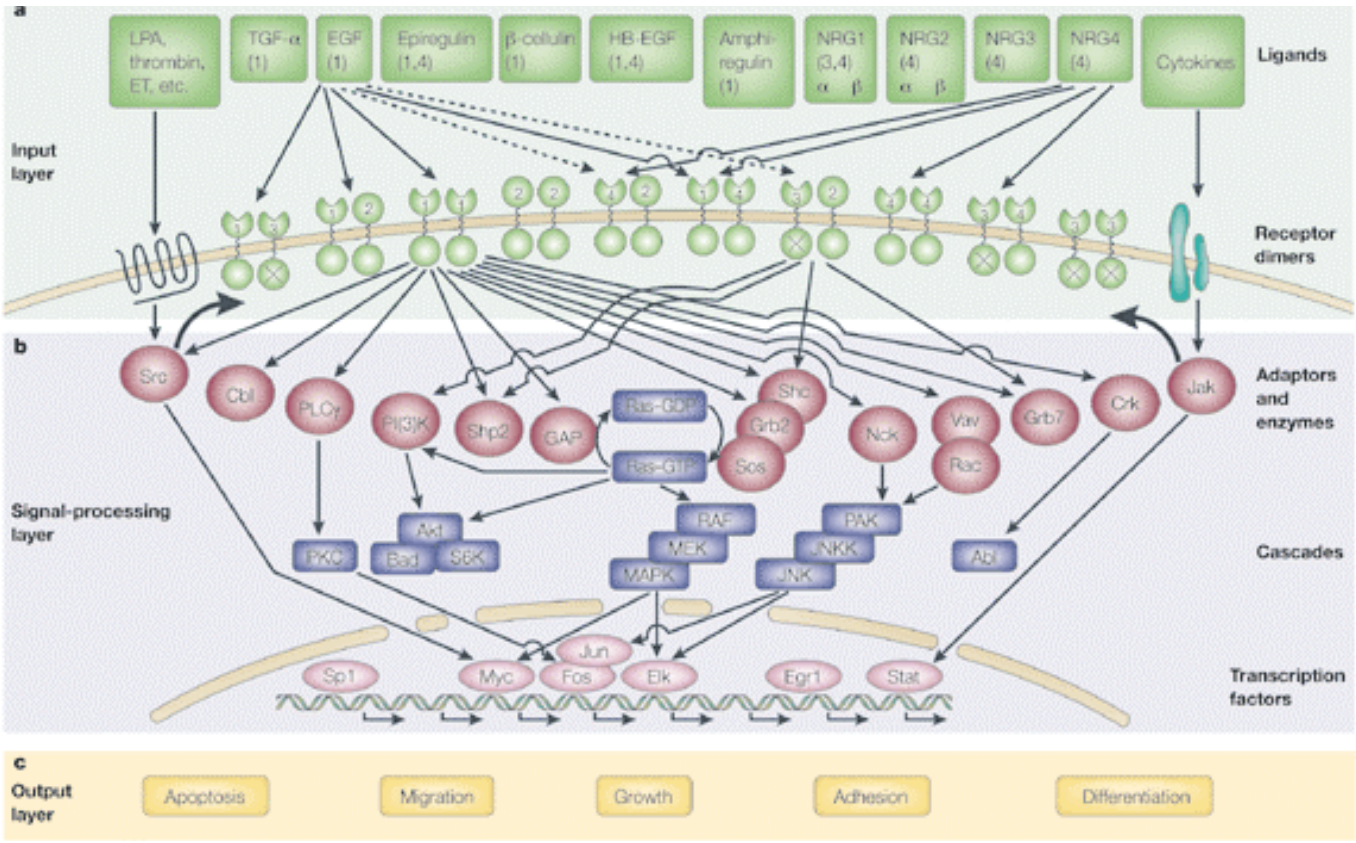

Fig. (1). Illustrative diagrams of different ligands that bind to the erbB receptor family leading to homo- or heterodimerization and activation of the receptors. Depending on the specific adaptor molecules recruited by erbB receptor activation, different signaling pathways are recruited for downstream signaling propagation leading to cellular and tissue effects including apoptosis, migration, growth, and differentiation. Numbers in parenthesis with the ligands indicate high affinity for the listed specific receptor subtypes. Reprinted by permission from Macmillan Publishers Ltd. Nat Rev Mol Cell Biol (Feb; 2(2): 127-137), copyright 2001.

approximately 70% and 30% of NSCLC cases respectively, but are rarely expressed in SCLC [9]. The crucial role of the EGFR pathway in NSCLC tumorigenesis renders it an appealing target for the development of targeted anticancer agents. The two main categories of molecularly targeted agents against EGFR are: a) monoclonal antibodies (MoAbs) against the receptor and b) tyrosine kinase inhibitors (TKIs). The action of these agents results in inhibition of downstream signal transduction (Fig. **1**).

A plethora of preclinical and clinical data supports the use of EGFR-targeting agents in human malignancies (Reviewed in [8]). Tables **1** and **2** summarize the most important phase III trials using EGFR-targeting agents in the first-line and second-line treatment of advanced NSCLC, respectively; Table **3** included two phase III trials with erlotinib as maintenance therapy in the treatment of advanced NSCLC.

3. MONOCLONAL ANTIBODIES AGAINST EGFR IN NSCLC

The chimeric monoclonal antibody IgG1 cetuximab and the fully humanized monoclonal antibody IgG2 panitumumab have been approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for the treatment of metastatic colorectal cancer [10, 11]. Cetuximab has been also approved for the treatment of head and neck cancer in combination with radiotherapy in the locally advanced setting [12] and as a single-agent for the treatment of platinum-refractory recurrent or metastatic head and neck cancer [13]. Preclinical studies with cetuximab have suggested that it can inhibit the growth of human NSCLC cell lines *in vitro* [14] and in athymic nude mice [15-17]. The initial evaluation of cetuximab as monotherapy in patients with advanced refractory NSCLC provided the earliest signal of its potential activity in NSCLC. Sixty-six patients were enrolled in a single arm phase II trial to receive cetuximab with a loading dose of 400 mg/m^2 and continuous weekly doses of 250 mg/m^2. The response rate was 4.5% (95% CI, 0.9% to 12.7%), stable disease rate 30.3% (95% CI, 19.6% to 42.9%), median time to progression (TTP) 2.3 months (95% CI, 2.1 to 2.6 months) and median overall survival (OS) 8.9 months (95% CI, 6.2 to 12.6 months). EGFR expression by immunohistochemistry failed to predict response to treatment with cetuximab [18]. Because of the limited efficacy of cetuximab as monotherapy subsequent studies evaluated this drug in combination with established cytotoxic agents. A number of other phase II clinical trials showed encouraging results with the addition of cetuximab to the combination of carboplatin with paclitaxel [19, 20] or docetaxel [21] in the first-line setting, reporting objective response (OR) rates as high as 57%, progression-free survival (PFS) of 4-6 months and median OS of 9-13 months. Similar results were reported when cetuximab was

Table 1. Major Phase III Clinical Trials with EGFR-Targeting Agents in the First-Line Treatment of Advanced NSCLC

Trial	Patient Number	Treatment Schema	PFS (Months)	OS (Months)	Comments
Pirker *et al*. 2009 [25]	1125	Cisplatin and vinorelbine plus cetuximab *vs* Cisplatin and vinorelbine	4.8 *vs* 4.8	11.3 *vs* 10.1	FLEX trial; although the study met its primary endpoint (OS), it did not show significant benefit in PFS
Lynch *et al*. 2010 [27]	676	Carboplatin and taxane (paclitaxel or docetaxel) plus cetuximab *vs* Carboplatin and taxane (paclitaxel or docetaxel)	4.4 *vs* 4.24	9.69 *vs* 8.38	BMS099 trial; failed to meet its primary endpoint (PFS) as assessed by independent radiologic review. There was a trend for improvement in OS similar to FLEX but the difference was not statistically significant.
Giaccone *et al*. 2004 [48]	1093	Cisplatin and gemcitabine plus gefitinib *vs* Cisplatin and gemcitabine	5.8 *vs* 6.0	9.9 *vs* 10.9	INTACT-1 trial
Herbst *et al*. 2004 [49]	1037	Carboplatin and paclitaxel plus gefitinib *vs* Carboplatin and paclitaxel	5.3 *vs* 5.0	9.8 *vs* 9.9	INTACT-2 trial
Gatzemeier *et al*. 2007 [50]	1172	Cisplatin and gemcitabine plus erlotinib *vs* Cisplatin and gemcitabine	5.9 vs 6.2	10.7 *vs* 11	TALENT trial; In a small group of patients who had never smoked, OS and PFS were increased in the erlotinib group
Herbst RS *et al*. 2005 [51]	1052	Carboplatin and paclitaxel plus erlotinib *vs* carboplatin and paclitaxel	5.5 *vs* 5.3	10.6 *vs* 10.5	TRIBUTE trial; patients who reported never smoking experienced improved OS in the erlotinib arm
Kobayashi *et al*. 2009 [46]	200	Gefitinib *vs* Carboplatin and Paclitaxel	10.4 *vs* 5.5	Not reported	Japanese study exclusively in patients with EGFR mutations; interim analysis for safety and efficacy
Lee *et al*. 2009 [45]	309	Gefitinib *vs* Cisplatin and Gemcitabine	6.1 *vs* 6.6	21.3 vs 23.3	FIRST-SIGNAL Trial; Asian population with clinical enrichment by restricting to never smokers;
Mok *et al*. [44]	1217	Gefitinib *vs* Carboplatin and Paclitaxel	5.7 *vs* 5.8	18.6 *vs* 17.3	IPASS Study; Asian patients, non-smokers or light smokers with adenocarcinoma (EGFR mutation not required)

combined with carboplatin and gemcitabine (median PFS, 5.3 months; median OS 10.3 months; one-year survival, 45%) [22]. A phase II randomized study on patients with EGFR positive tumors, as assessed by immunohistochemistry, evaluated cisplatin and vinorelbine with the same regimen plus cetuximab and suggested that the addition of the monoclonal antibody may lead to better outcomes (median PFS, 5.0 *vs* 4.6 months; median OS, 8.3 *vs* 7.3 months) [23]. In another randomized phase II study of gemcitabine plus cisplatin or carboplatin with or without cetuximab, the addition of cetuximab also seemed to improve outcomes in terms of PFS (5.1 *vs* 4.2 months) and median OS (12 *vs* 9.3 months) [24].

In a large multi-national, multicentre, open-label, phase III trial (FLEX trial), 1125 chemotherapy-naive patients with advanced, EGFR-expressing (as evaluated by immunohistochemistry), stage IIIB / IV NSCLC were randomly assigned to platinum-based chemotherapy plus cetuximab (n=557) versus chemotherapy alone (n=568) [25]. Chemotherapy consisted of cisplatin 80 mg/m^2 on day 1 and vinorelbine 25 mg/m^2 on days 1,8 every 3 weeks for up to six cycles. Cetuximab was administered on a standard dosing regimen (400 mg/m2 intravenous infusion over 2 hours on day 1, and from day 8 onwards at 250 mg/m2 over 1 hour per week) and continued as maintenance after the end of chemotherapy until disease progression or unacceptable toxicity had occurred. The primary endpoint of this trial was overall survival. Patients in the chemotherapy plus cetuximab arm survived longer than those in the chemotherapy-alone group (median 11.3 months *vs* 10.1 months; hazard ratio (HR) for death 0.871 [95% CI 0.762-0.996]; *P*=0.044). As expected, the rate of grade 3 and 4 rash, infusion-related reactions, and diarrhea were more common with chemotherapy plus cetuximab. The rate of neutropenic fever and septic complications were also higher with the addition of cetuximab to cisplatin/vinorelbine but the number of treatment-related deaths was similar between the two arms (3% *vs* 2%). The magnitude of EGFR expression did not predict response to treatment in the experimental arm suggesting that patients with EGFR-expressing NSCLC derived clinical benefit from the addition of cetuximab independent of the level of EGFR expression

Table 2. Major Phase III Clinical Trials with EGFR-Targeting Agents in the Second-Line Treatment of Advanced NSCLC

Trial	Patient Number	Treatment Schema	PFS (Months)	OS (Months)	Comments
Shepherd *et al*. 2005 [41]	731	Erlotinib *vs* Placebo	2.2 *vs* 1.8	6.7 *vs* 4.7	BR.21 trial; Patients with stage IIIB or IV NSLC; First trial with survival benefit with an EGFR-TKI
Thatcher *et al*. 2005 [36]	1692	Gefitinib *vs* placebo	3.0 *vs* 2.6	5.6 *vs* 5.1	ISEL trial; Failed to meet its primary survival endpoint (OS). Preplanned subgroup analyses showed significantly longer survival in the gefitinib group than the placebo group for never-smokers and patients of Asian origin
Kim *et al*. 2008 [37]	1466	Gefitinib *vs* docetaxel	3.1 vs 3.0	7.6 *vs* 8.0	INTEREST study; showed non-inferiority of gefitinib in terms of OS in second line treatment

[26]. Moreover, neither K-ras mutation status nor EGFR gene copy number predicted a subset of patients that benefit more from the addition of cetuximab to chemotherapy [26]. It is noteworthy, however, that despite the significant overall survival advantage in cetuximab-treated patients, the FLEX trial failed to show significant difference in PFS (4.8 months in both groups; HR: 0.943, 95% CI 0.825–1.077; *P*=0.39). The authors attributed this to the different censoring patterns between the two treatment arms since more patients in the chemotherapy-alone group started another anticancer treatment before progressive disease was radiologically documented. Analysis of time-to-treatment failure as a posthoc sensitivity analysis for PFS showed a significant benefit with chemotherapy plus cetuximab [25].

Another phase III randomized trial (BMS099) evaluated the potential benefit of adding cetuximab to the combination of paclitaxel or docetaxel and carboplatin for unselected patients with advanced NSCLC. Although there was a significant increase in OR rate with the triplet combination, the study failed to show an improved PFS as assessed by independent radiologic review which was its primary endpoint [27]. Median OS was 9.69 months with the triplet combination and 8.38 months with the doublet (HR: 0.89; 95% CI 0.754 to 1.051; *P* =0.169) but the study lacked the statistical power to show a 1-month difference in overall survival [27]. Similar to the FLEX trial, no molecular markers that could enable the selection of patients most likely to benefit from cetuximab treatment were identified [28]. Of interest, however, is the observation that the 185 patients assigned to the cetuximab arm (58.7% of the total study population) who experienced acneiform rash of any grade on day 21 from enrolment achieved a median survival of 10.4 months (95% CI, 7.7-12.0) compared to 8.9 months (95% CI, 6.8-10.9) for the 130 patients who were assigned in the same arm but did not have early onset rash (HR: 0.76; 95% CI, 0.59-0.98) [29]. A recently reported meta-analysis on 2,018 patients from four randomized controlled phase II/III studies with chemotherapy with or without cetuximab demonstrated a significant benefit across all investigated efficacy endpoints for the cetuximab combination over chemotherapy alone: OS (HR: 0.878, 95% CI 0.795–0.969, *P*=0.01), PFS (HR: 0.899, 95% CI 0.814–0.993, *P*=0.036) and OR (HR: 1.463, 95% CI 1.201–1.783, *P*<0.001) [30].

There are several outstanding issues regarding the optimal integration of cetuximab in the first-line treatment of advanced NSCLC. First, the platform regimen used in FLEX is a cisplatin-based doublet that is rarely employed by medical oncologists in the US. BMS099 that used carboplatin and paclitaxel showed a similar difference in median survival between the cetuximab and control arms but the *P* value did not reach statistical significance presumably because this study was about half the size of FLEX and was not powered to detect such a small difference. Second, it is unclear whether selection on the basis of EGFR by immunohistochemistry should be applied in clinical practice, although the requirement of at least one positive cell in the FLEX trial excluded only a small fraction of patients (about 15%). Moreover, because of the small magnitude of survival benefit (about one-month improvement in median survival) the corresponding costs for each year of life saved can become substantial [31]. Better ways of patient selection may improve the cost/benefit ratio. In conclusion, the addition of cetuximab may be considered as a therapeutic option but its use cannot be widely or strongly recommended at this time. An important ongoing phase III trial led by the South West Oncology group (SWOG) is based on prior

Table 3. Phase III Clinical Trials with EGFR-Targeting Agents as Maintenance Therapy of Advanced NSCLC

Trial	Patient Number	Treatment Schema	PFS (Months)	OS (Months)	Comments
Cappuzzo *et al*. 2009 [54]	889	Erlotinib *vs* placebo	3 *vs* 2.7	12 *vs* 11	SATURN trial; benefit of erlotinib across ethnic groups, tumor histologies and smoking status.
Miller *et al*. 2009 [55]	768	Erlotinib plus bevacizumab *vs* bevacizumab	4.76 *vs* 3.75	NR	ATLAS trial; improved PFS (closed early) but still immature for OS analysis

promising efficacy results with carboplatin/paclitaxel/ bevacizumab and cetuximab [32] and the potential importance of *EGFR* FISH as a predictor of outcome (which does not mirror the biomarker analysis of FLEX though) [33]. This large study will compare carboplatin and paclitaxel with or without cetuximab (bevacizumab is allowed in both arms for patients eligible to receive it) and is powered to evaluate outcomes in the subset of *EGFR* FISH positive tumors (NCT00946712). It is expected that the results of this phase III study will define the future role of cetuximab in the first-line treatment of NSCLC.

4. EGFR TYROSINE KINASE INHIBITORS IN NSCLC

4.1. EGFR-TKIs as Monotherapy in Second-Line Treatment

Receptor TKs are membrane-associated glycoproteins that are activated following ligand binding. Abnormal TK activity may result from receptor overexpression, increased ligand availability or constitutive activation of the enzyme through mutation in the gene sequences of the receptor itself [5]. Gefitinib was the first EGFR-TKI tested in clinical trials. Two multicenter phase II trials (IDEAL-1 and IDEAL-2) evaluated gefitinib monotherapy in advanced NSCLC patients who had progressed on cytotoxic chemotherapy and reported promising results with RR ranging between 9% and 18% and overall disease control rate of 43%–50% [34, 35]. The follow-up ISEL (Iressa® Survival Evaluation in Lung cancer) trial was designed as a confirmatory phase III trial that randomized nearly 1700 patients with previously treated advanced NSCLC to gefitinib or placebo. At a median follow-up of 7.2 months, median survival did not differ significantly between the groups in the overall population (5.6 months for gefitinib and 5.1 months for placebo; HR: 0.89, *P*=0.087) or among the 812 patients with adenocarcinoma (6.3 months *vs* 5.4 months; HR: 0.84, *P*=0.089). Although the study failed to meet the target survival benefit endpoint, preplanned subgroup analysis showed significantly longer survival in the gefitinib group compared to the placebo group for never-smokers (n=375; HR: 0.67, *P*=0.012; median survival 8.9 *vs* 6.1 months) and patients of Asian origin (n=342; HR: 0.66, *P*=0.01; median survival 9.5 *vs* 5.5 months) [36]. Reasons for the negative outcome remain unsettled but the dose selected for the phase III trial and the ethnic mix of the selected patient population possibly contributed to this outcome. Gefitinib remains in clinical use, predominantly in Asia, although in the United States it is currently indicated only for NSCLC patients who have previously benefited from gefitinib treatment or patients receiving gefitinib in the context of a clinical trial.

More recent data have supported the use of gefitinib in the second-line therapy of NSCLC. The INTEREST [37] trial was a phase III trial comparing gefitinib to docetaxel as second-line therapy. The trial showed non-inferiority of gefitinib versus docetaxel in terms of OS in the overall study population by meeting the predefined non-inferiority endpoint (median survival 7.6 *vs* 8.0 months, HR: 1.02, 95% CI 0.905-1.150). Subset analysis for patients with adequate tissue samples showed that overall survival was similar in the gefitinib and docetaxel arms for any of the biomarker subgroups analysed, including EGFR protein expression, *EGFR* gene copy number and *EGFR* mutation status [38]. Finally, in another randomized phase III study conducted in Japan, gefitinib improved quality of life over docetaxel, as second-line treatment with superior OR rate and a more favorable tolerability profile and no statistically significant difference in OS (although non-inferiority was not statistically proven) [39].

Erlotinib is another EGFR-TKI with significant clinical activity in NSCLC. Erlotinib was tested in a randomized phase III trial for the second- and third-line treatment of NSCLC. In the BR.21 trial conducted by the National Cancer Institute of Canada Clinical Trials collaborative group, 731 patients with stage IIIB or IV NSCLC were randomized to receive erlotinib or placebo. Patients in the experimental arm had RR of 8.9% compared to less than 1% in the placebo group (P<0.001); median PFS was 2.2 months and 1.8 months (HR: 0.61, adjusted for stratification categories; *P*<0.001) and median OS was 6.7 months and 4.7 months (HR: 0.70; *P*<0.001) in the erlotinib and placebo arm, respectively [40]. The demonstrated clinical efficacy in this phase III trial led to erlotinib approval by the United States FDA.

The toxicity profile of gefitinib and erlotinib is well characterized and includes rash and diarrhea as the predominant toxicities. Nevertheless, rare and potentially life-threatening complications, such as interstitial lung disease [41], have been described.

4.2. EGFR-TKIs as Monotherapy in First-Line Treatment

Based on the positive results achieved with EGFR-TKIs in the second- and third-line therapy settings, studies of these agents were conducted as first-line therapy in selected patients with advanced NSCLC. A consistent finding throughout EGFR-TKI studies was that patients with certain clinical characteristics, such as never or light smokers, female patients and patients of Asian ancestry, and those with adenocarcinoma histology had high response rates to EGFR-TKIs. Therefore, these patients were selected for first-line therapy studies with EGFR-TKIs in NSCLC. Moreover, it became apparent that the efficacy of EGFR-TKIs in these patients could be, at least partially, attributed at the presence of *EGFR* activating mutations, the most common of which are substitution mutations (L858R) in exon 21 or deletion mutations (delE746-A750) in exon 19 of the *EGFR* gene. A single arm phase II study confirmed the activity of gefitinib as monotherapy in the frontline setting in patients with advanced NSCLC harboring somatic EGFR mutations, reporting ORR of 55% (95% CI, 33 to 70) and median progression-free survival of 9.2 months (95% CI, 6.2 to 11.8) [42]. Of note, a recent study conducted by the Spanish lung cancer working group showed that large-scale screening of patients with lung cancer for *EGFR* mutations is feasible and could potentially play a role in therapeutic decisions [43]. EGFR mutations were identified in 350 of 2105 screened patients (16.6%). The median PFS and OS for 217 patients who received erlotinib were 14 months and 27 months, respectively.

The provocative efficacy outcomes with EGFR-TKI monotherapy in selected patients prompted the design of several phase III randomized trials of an EGFR-TKI versus standard cytotoxic chemotherapy in the frontline setting in a clinically enriched or molecularly selected NSCLC patient population. The "First Line Iressa versus

Carboplatin/Paclitaxel in Asia" (Iressa Pan Asian Study" [IPASS]) and the "First-line Single Agent Iressa versus Gemcitabine and Cisplatin Trial in Never-smokers with Adenocarcinoma of the Lung" (FIRST-SIGNAL) are two clinical trials conducted in Asia with great potential to change the treatment paradigm for NSCLC patients [44, 45]. Both studies compared gefitinib at the 250 mg approved dose in Asia against a platinum-based doublet. The IPASS study used clinical predictor of response (nonsmoker or former light smokers) to select patients with advanced pulmonary adenocarcinoma for enrolment in the trial [44]. The study not only met its primary objective of demonstrating non-inferiority of gefitinib but also showed its superiority, as compared with the carboplatin-paclitaxel combination, with respect to PFS (HR, 0.74; 95% CI: 0.65 to 0.85; $P<0.001$). In a subgroup of 261 patients with confirmed *EGFR* mutation, PFS was even more longer among those who received gefitinib than among those who received carboplatin-paclitaxel (HR, 0.48; 95% CI, 0.36 to 0.64; $P<0.001$), whereas in the subgroup of 176 patients who were negative for the mutation, PFS was significantly longer with carboplatin-paclitaxel treatment (HR, 2.85; 95% CI, 2.05 to 3.98; $P<0.001$). Overall survival in this early analysis (450 patients [37.0%] died, with follow-up ongoing) was similar between the two groups in the overall population (HR for death in the gefitinib group, 0.91; 95% CI, 0.76 to 1.10). Median survival was 18.6 months among patients receiving gefitinib and 17.3 months among patients receiving carboplatin–paclitaxel [44]. In subset analysis, the HR with gefitinib was 0.78 (95% CI, 0.50 to 1.20) in the mutation-positive subgroup and 1.38 (95% CI, 0.92 to 2.09) in the mutation-negative subgroup. Finally, significantly more patients in the gefitinib group had a clinically relevant improvement in quality of life, as assessed by scores on the FACT-L questionnaire (odds ratio, 1.34; 95% CI, 1.06-1.69, $P=0.01$) [44].

In conclusion, the IPASS trial showed that gefitinib is superior to cytotoxic chemotherapy in the frontline treatment of advanced lung adenocarcinoma in Asian non-smokers or former light smokers in terms of RR and PFS. Molecular analysis suggested that the benefit in PFS can be primarily attributed to the effect in patients with *EGFR* mutation positive tumors. However, chemotherapy may be preferable for patients with tumors not harboring an EGFR mutation [44].

The FIRST-SIGNAL study [45] also employed clinical enrichment by enrolling 313 never smokers with chemotherapy-naïve stage IIIB/IV lung adenocarcinoma. Patients were randomized to receive either gefitinib (250 mg) or cisplatin and gemcitabine. Consistent with the IPASS data, patients on the gefitinib arm had a numerically higher OR than the chemotherapy arm (53.5% *vs* 42.0%; $P=0.0811$) and significant improvement in PFS (HR, 0.737; 95% CI, 0.580-0.938; $P=0.0063$). There was, however, no significant survival advantage between the two arms, (20.3 months *vs* 23.1 months; HR: 1.029, 95% CI: 0.756-1.401, $P=0.4278$) presumably because 80% of all patients on the chemotherapy arm eventually received gefitinib off study following disease progression. Subset analysis of the limited number of patients with known EGFR mutation status showed that the benefit of gefitinib therapy was mainly observed in those with *EGFR* mutant tumors. Median PFS was significantly better in the mutation-positive patients compared with the mutation-negative on the gefitinib arm (7.9 months *vs* 2.1 months; HR: 0.385, 95% CI: 0.208-0.711, $P=0.009$) but no similar interaction was observed in the chemotherapy arm (median 5.8 months *vs* 5.5 months; HR: 1.223, 95% CI: 0.650-2.305, $P=0.2657$) [45].

The impressive activity of EGFR-TKIs in clinically-enriched patient population primarily results from the higher prevalence of *EGFR* mutant tumors in such patient populations. Therefore, it is reasonable to attempt to select patients based on the presence of *EGFR* mutations. A prospective study to compare frontline EGFR-TKI with chemotherapy in advanced NSCLC patients with EGFR mutant tumors was conducted by the North East Japan Gefitinib Study Group [46]. The study was designed to randomly assign 300 patients with stage IIIB/IV NSCLC to either receive gefitinib or paclitaxel/carboplatin doublet in a 1:1 fashion. A planned interim analysis 4 months after enrolling the initial 200 patients showed the superiority of gefitinib over carboplatin/paclitaxel in terms of RR (74.5% *vs* 29%, $P=0.001$) and PFS (10.4 months *vs* 5.5 months, HR: 0.357, 95%CI: 0.25-0.51, $P<0.001$). The study was therefore closed to further patient accrual but OS data is still awaited. In another, recently reported study from Japan (WJTOG 3405), among 177 chemotherapy-naive patients diagnosed with stage IIIB/IV NSCLC or postoperative recurrence harboring *EGFR* mutations (either the exon 19 deletion or L858R point mutation), those treated with gefitinib had significantly longer PFS compared to those treated with cisplatin plus docetaxel [47]. Based on the data above it is recommended to use an EGFR-TKI for the treatment of patients with an *EGFR* activating mutation. This recommendation is based on the superior OR and PFS data with an EGFR-TKI versus standard chemotherapy and the preferable toxicity profile of EGFR-TKIs. Although an advantage in OS has not been demonstrated yet, this would be difficult because of the major effect of crossover to second-line therapy with EGFR-TKI in patients with EGFR mutations who receive chemotherapy initially. Nevertheless, it is appropriate, and now a common practice in many institutions, to routinely test selected NSCLC (e.g. adenocarcinomas) for an EGFR activating mutation.

4.3. EGFR-TKIs in Combination with Chemotherapy

A combination strategy with cytotoxic chemotherapy was pursued in the first-line treatment setting but without success. Two large randomized phase III trials that combined gefitinib with chemotherapy (cisplatin/gemcitabine for the INTACT-1 and paclitaxel/carboplatin for the INTACT-2 trial) in the first-line setting did not show any survival benefit [48, 49]. Similar in design to the INTACT trials, the TALENT and TRIBUTE trials are two large phase III trials that evaluated whether the addition of erlotinib to a platinum based doublet (cisplatin/gemcitabine, TALENT trial) or (carboplatin/paclitaxel, TRIBUTE trial) in the frontline setting could result in survival advantage. This strategy also failed to produce any survival improvement [50, 51]. There was, however, a beneficial effect in subset analysis in patients with *EGFR* mutant tumors who remained on prolonged erlotinib following completion of combined erlotinib and chemotherapy. An ongoing phase II randomized trial by CALGB will evaluate erlotinib versus

erlotinib plus carboplatin and paclitaxel in never or light smokers with adenocarcinoma histology (CALGB-30406; NCT00126581). It has been proposed that simultaneous administration of an EGFR-TKI results in G1 cell cycle arrest which leads to resistance to chemotherapy, thus having an antagonizing effect. A number of clinical studies have attempted to overcome hypothesized resistance by the intermittent administration of EGFR-TKIs with chemotherapy in order to achieve pharmacodynamic separation and potentially improve antitumor efficacy [52]. A phase II trial randomized 143 patients with *EGFR* FISH or EGFR immunohistochemistry positive NSCLC to receive either intercalating chemotherapy with erlotinib or erlotinib alone [53]. There was no difference in outcome on the basis of *EGFR* FISH positivity. More importantly, it appeared that patients with activating *EGFR* mutations do not benefit from the addition of chemotherapy to erlotinib.

4.4. EGFR-TKIs as Maintenance Therapy for Advanced NSCLC

The role of EGFR-TKIs as maintenance therapy has also been evaluated in randomized trials. In the TALENT study [50], prolonged therapy with erlotinib delayed disease progression which supported the rationale for evaluating erlotinib in the maintenance setting. SATURN [54] was a randomized phase III trial that assessed the clinical benefit of erlotinib as maintenance therapy in non-progressing patients following completion of four cycles of frontline platinum-based doublet therapy (choice of chemotherapy regimen was at the discretion of the investigator). Eight-hundred–and-eighty-nine out of 1949 patients (46%) with advanced NSCLC remained progression-free at completion of four cycles of frontline chemotherapy and were randomly assigned to receive either erlotinib or placebo until the development of intolerable toxicity or disease progression. Patients on the erlotinib arm achieved better outcome in terms of RR (12% versus 5%), PFS (12 weeks versus 11.1 weeks; HR, 0.71; 95% CI, 0.62-0.82; $P<.0001$) and OS (12 months versus 11 months; HR, 0.81; 95% CI, 0.70–0.95; $P=0.0088$). Biomarker and subset analysis showed that the benefit of maintenance erlotinib extends across ethnic groups, tumor histologies and smoking status [54]. Only a small proportion of patients (16%) on the placebo arm received post-study erlotinib. On the basis of these results, the FDA approved erlotinib as monotherapy for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. Gefitinib was also evaluated as maintenance therapy after platinum-based chemotherapy in a placebo-controlled phase III Japanese trial [55]. This trial that randomized 603 patients with advanced NSCLC demonstrated prolonged PFS (HR, 0.68; 95% CI, 0.57- 0.80; $P<0.001$) but not OS (P=0.10) with the use of gefitinib. However, in a pre-specified analysis of OS by histology, gefitinib improved OS in patients with adenocarcinoma histology (n=467; HR, 0.79; 95% CI, 0.65-0.98; $P=0.03$).

The ATLAS study [56] sought to build on the survival advantage achieved with the addition of bevacizumab to frontline chemotherapy followed by maintenance bevacizumab by the addition of erlotinib [57]. This phase III randomized study enrolled 1160 patients for frontline therapy with platinum-based doublet chemotherapy along with bevacizumab. At completion of 4 cycles of chemotherapy, 768 non-progressing patients were randomized in a 1:1 fashion to receive bevacizumab alone or bevacizumab in combination with erlotinib. With a median PFS of 4.76 months versus 3.75 months (HR: 0.722; CI 0.592-0.881; $P<0.0012$) in favor of the erlotinib plus bevacizumab arm, the study met its primary objective and was closed early. Approximately 40% of patients subsequently received erlotinib as second-line therapy in both arms of the ATLAS study. OS data have not been reported yet from this study, however, it may have been underpowered to detect a significant difference in OS [56]. Based on these results, the use of erlotinib as a maintenance therapy should come under consideration as a therapeutic option for patients with good performance status who respond to first-line chemotherapy. However it is also recognized that the survival benefit by erlotinib maintenance seen in the SATURN study is rather small and might have been counter-balanced by the use of erlotinib at progression.

5. FUTURE PERSPECTIVES AND CONCLUSIONS

Ongoing research has made apparent that lung cancer is a heterogeneous disease that requires a multi-disciplinary approach and an individualized therapeutic strategy. It is anticipated that emerging data will provide the foundation for a molecular classification of lung cancer that will complement or replace histological and clinical classifications. Currently, the histological subtype of NSCLC as well as the presence of *EGFR* gene mutations have become important predictive tools that assist clinicians in treatment decisions.

Although EGFR-targeting therapies (erlotinib, gefitinib, cetuximab) have earned a place in the armamentarium for NSCLC, the most appropriate use of these agents in the era of personalized medicine continues to evolve. Current evidence suggests that EGFR mutations can be used for the selection of patients for first-line treatment with EGFR-TKIs. Novel ways of inhibiting the EGFR pathway are being explored. Second-generation EGFR-TKIs, such as BIBW-2992, a dual EGFR/HER-2 inhibitor that may be active against tumors with the secondary T790M point mutation, which is associated with acquired resistance to gefitinib and erlotinib, are under development. Combinations of EGFR inhibitors with other classes of targeted agents, such as angiogenesis inhibitors, are of interest for the treatment of advanced NSCLC and evaluated in clinical trials. Continued clinical research incorporating molecular methodologies and pharmacogenomic analysis is needed to further delineate the role of EGFR inhibitors alone or in combination for the treatment of NSCLC.

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