Review Article

# Optimizing the use of epidermal growth factor receptor inhibitors in advanced non-small-lung cancer (NSCLC)

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**ABSTRACT** Lung cancer is the leading cause of cancer-related death in US and Europe. Treatment with a platinum-based chemotherapy remains the standard of care, however with modest effect on quality of life and overall survival which seldom reaches 1 year. Recently, several classes of targeted agents have emerged showing promising results. In particular, agents targeting the epidermal growth factor receptor (EGFR) showed impressive clinical activity both in the first line and salvage settings. However, it is evident that these drugs are not effective in all patients. Putting into consideration the very high cost of these agents, there is an urgent need to provide reliable tools to identify those patients that would derive the maximum benefit from these drugs. Several predictive biomarkers were developed to identify those patients who would derive the maximal benefit of these drugs. In this review we will discuss the recent updates on the role of EGFR inhibitors in the treatment of advanced NSCLC and the role of predictive bio-markers in patient selection.

**Key Words:** advanced NSCLC; gefitinib; erlotinib; EGFR; biomarkers; cetuximab

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## Introduction

Lung cancer is the most common cancer and the leading cause of cancer-related deaths in US and Europe (1-3). NSCLC accounts for 85% of all lung cancers and is often diagnosed at an advanced stage with poor prognosis (2). Palliative chemotherapy is associated with modest survival benefit and improved quality of life (4,5). Based on the results of several large phase III randomized trials, platinum-based doublet chemotherapy has become the standard of care with a median survival barely reaching one year (6-10). Non-platinum containing regimens showed similar efficacy but at the expense of a higher cost (11). The addition of third chemotherapeutic agent to the platinum based doublets did not demonstrate a significant improvement in survival (12,13). Recent studies have addressed the role of maintenance therapy following four cycles of chemotherapy with significant improvement observed in progression-free survival (PFS) but no impact on overall survival (OS) (14).

The role of chemotherapy in second line therapy is even less impressive with docetaxel and pemetrexed demonstrating a PFS of 3 months and OS not exceeding 8 months (15,16). Hence, a plateau has been reached with respect to the chemotherapy benefit. Furthermore, elderly patients and those with poor performance status, which constitute a large fraction of NSCLC patients, cannot tolerate these drugs at recommended doses. This necessitated the incorporation of newer agents with different toxicity profiles and mechanisms of action.

NSCLC is frequently associated with EGFR over expression, which occurs in 40–80% of patients (17-20). EGFR has a role in activating two major pathways in solid tumors, the PI3K/AKT/mTOR pathway, and the RAS/RAF/MEK/MAPK pathway (21). These signaling pathways are important in tumor cell growth, local invasion, angiogenesis, protein translation and cell metabolism (22).

## EGFR targeting therapies

EGFR is a member of the EGFR tyrosine kinase family, which consists of EGFR (ErbB1/HER1), HER2/neu (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). All the family members contain an extracellular ligand-binding domain (domains I, II, III, IV), a single membrane-spanning region, a juxta-membrane nuclear

No potential conflict of interest.

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localization signal and a cytoplasmic tyrosine kinase domain with the exception of ErbB3, which lack an intracellular tyrosine kinase activity (23). EGFR receptors are expressed in various cell types; but primarily in those of epithelial, mesenchymal and neuronal origin (24). Upon activation, EGFR activates many complex intra cellular signaling pathways that are tightly regulated by the presence and identity of the ligand, heterodimer composition, and the availability of phosphotyrosine-binding proteins (25). In this review, we will discuss in details the results of three agents that are advanced in clinical development, namely erlotinib, gefitinib and cetuximab. We will highlight the progress in their clinical development and the potential role of biomarkers in predicting response and clinical outcome.

## Early data with EGFR tyrosine kinase inhibitors (TKI)

### Gefitinib (Iressa®)

Gefitinib is an orally active, reversible HER-1/EGFR tyrosine kinase inhibitor. It demonstrated promising activity in the second-line and third-line treatment in unselected NSCLC patients in two large phase II trials (IDEAL I & IDEAL II) using two different doses (250mg/d and 500 mg/d). Both studies showed similar results with a response rate (RR) ranging from 9–19%, PFS of 2.7–2.8 months and OS of 6–8 months (26,27).

Based on the promising results of IDEAL I &II; a large phase III trial (ISEL) was conducted and 1,692 patient were enrolled in this trial. The trial compared gefitinib (500mg/m2) to placebo in unselected, previously treated patients with advanced NSCLC (28). The results were disappointing with no differences observed in median survival between both arms (5.6 months vs 5.1 months, P = 0.087). However, a subgroup analysis demonstrated a significantly longer median survival for the gefitinib arm in never-smokers (8.9 months vs 6.1 months, P = 0.012) and in patients of Asian origin (9.5 months vs 5.5 months, P = 0.01) (28).

In a retrospective effort attempted to identify the possible predictors of better outcomes; EGFR mutations were detected in 12% of tested samples (tissue samples were only available in 27% of cases) and a striking difference in RR with gefitinib was observed in that patient population compared with patients with wild-type EGFR. However the numers were too low to demonstrate impact on survival (29).

Later two studies investigated the addition of gefitinib to standard chemotherapy, either cisplatin/gemcitabine (INTACT 1) (30), or carboplatin/paclitaxel (INTACT 2) (31) in chemo-naive patients with advanced NSCLC. Both studies were negative with no improvement observed in RR, PFS or OS.

### Erlotinib (Tarceva®)

Another EGFR TKI, erlotinib, gained the Food and Drug Association (FDA) and European medicines agency (EMEA) approval on the basis of results of a large phase III trial (BR21), which demonstrated a survival advantage for erlotinib compared to placebo (6.7 months vs 4.7 months, Hazard Ratio [HR] 0.70, P < 0.001) (32) in patients previously treated with platinum-based chemotherapy. The study had an almost similar design to that of the ISEL trial. However, it is important to note that in the BR21 study; around 40% of patients were previous responders to chemotherapy; while only 20% of patients enrolled in the ISEL trial responded previously to chemotherapy. This might reason the differences in the results obtained between the two studies (33).

In a subgroup analysis of the BR21 study, erlotinib yielded better results in females, non-smokers, and in patients with adenocarcinomas. On the other hand, male smokers with squamous-cell carcinoma were the most disadvantaged population (34). In a similar way to the ISEL trial; the expression of EGFR, EGFR copy number, and EGFR mutational status were retrospectively evaluated (35). EGFR expression was evaluated by immunohistochemistry (IHC) in specimens of 325 patients out of 731 patients participated in the trial. One hundred and ninety seven samples were analyzed for EGFR mutations; and 221 samples were analyzed for the number of EGFR genes. In the univariate analyses, survival was longer in the erlotinib group when EGFR was expressed (HR, 0.68; P = 0.02) or high EGFR gene copy number (HR, 0.44; P = 0.008). In multivariate analyses, adenocarcinoma (P = 0.01), non-smokers (P < 0.001), and EGFR expression by IHC (P=0.03) were predictive for higher response rate. However the OS was not influenced by the status of EGFR expression, the number of EGFR copies, or EGFR mutation (35).

In a similar strategy to gefitinib; erlotinib also failed to provide benefit when tested in combination with chemotherapy in two large, randomized trials (36,37). However, a survival benefit was observed in patients who had never smoked (23 months in patients on erlotinib with chemotherapy vs 10 months in the same population treated with carboplatin and paclitaxel only) (38). Patients with EGFR mutations had overall better outcomes irrespective of treatment arm (39). A higher RR and trend to better time to progression was observed in patients with EGFR mutations treated with erlotinib compared with chemotherapy. These results were, however, not definitive as the trial was neither designed nor powered to examine this correlation.

## Lessons learned from the EGFR TKI early studies

Perhaps the hallmark of the former studies was observing fascinating durable responses in a minority of patients. This was consistent for erlotinib and gefitinib. It was clear that non-smokers and those with non-squamous histology benefit the

most. However, it was not quite clear the reason behind this association. Thus, it was clear that we need to identify this subgroup that derives the maximum benefit out of these agents.

A very interesting point is that EGFR TKIs may also antagonize chemo therapy effects by blocking cells in the G1 phase of the cell cycle, and they might also interfere with platinum uptake into tumor cells, possibly by decreasing expression of membrane uptake transporters (40,41). Thus an understanding of the specific molecular features that contribute to EGFR TKI resistance was definitely needed.

The discovery of molecular aberrations, such as MET kinase amplification or mutation and EML4-ALK fusion, which cause constitutive activation of RAS/RAF/MEK, has provided further insights into factors limiting the therapeutic efficacy of EGFR inhibitors (42-44). Other mechanisms underlying the low overall efficacy of anti EGFR TKIs could be related to EGFR functions other than activating signaling pathways. These functions include the kinase-independent activity of EGFR in maintaining cancer cell survival, and its importance in the co expression of the sodium/glucose co transporter (SGLT1), which supplies basic energy needs to cancer cells irrespective of extracellular and intracellular glucose levels (45). In the presence of an EGFR TKI, the metabolic activity of cancer cells is decreased, but cell death does not occur. Only down regulation of EGFR (and not just inhibition of its tyrosine kinase) could cause disruption of SGLT1 activity, which led to autophagic cell death in a preclinical setting (45).

## Towards optimizing the use of EGFR TKI: the start of an era

Based on the fact that EGFR TKI (gefitinib and erlotinib) showed promising efficacy in Asian patients with advanced adenocarcinoma and given that older population are in need of less toxic therapies, several phase II trials investigated the use of gefitinib or erlotinib as a first line monotherapy in older population with advanced NSCLC of Asian ethnicity.

From January 2002 to December 2005; 55 patients with advanced adenocarcioma and a median age of 73.5 years were randomized (2:1) to either a platinum based doublet or gefitinib 250 mg daily. There was no statistical significance between the 2 groups for efficacy, PFS and OS in both arms (46). Similar results were observed in other phase II and in non-Asian population as well (47-49).

Toward a real step to tailoring therapy in lung cancer; the Iressa Pan-Asia Study (IPASS) was conduced. Based on a non inferiority concept; Mok et al hypothesized that first-line EGFR TKI would be at least equally effective as chemotherapy in a clinically selected population with a high incidence of EGFR mutations estimated that if 50% of the highly selected population harbor an EGFR mutation, the RR should be equal to the Paclitaxel/Carboplatin combination (50). The targeted population was none or light smokers from Asia with adenocarcinoma with a primary endpoint of PFS. Between March 2006 and October 2007; a total number of 1,217 patients were enrolled from 9 Asian countries. Patients were randomized to receive gefitinib (n=609) or carboplatin/paclitaxel (n = 608). Gefitinib demonstrated superior PFS and RR compared with chemotherapy ([HR] 0.74; 95% CI: 0.65-0.85; P<0.0001) and (43% vs 32.2%; odds ratio [OR] = 1.59; 95% CI: 1.25-2.01; P = 0.0001) respectively.

Tumor samples from 437 patients were evaluated for EGFR mutation and 261 (59.7%) positive samples were found, among which 140 (53.6%) were positive for exon 19 deletion and 111 (42.5%) were positive for exon 21 L858R mutations. The RR to gefitinib was 71.2% for patients with an EGFR mutation but as low as 1.1% for tumors not harboring the mutation. On the other hand, the RR to chemotherapy was 47.3% and 23.5%, respectively. PFS in EGFR mutation-positive patients was longer with gefitinib compared to chemotherapy (HR = 0.48; 95% CI: 0.36-0.64; P<0.0001) while in EGFR mutation-negative patients, PFS was longer with chemotherapy than with gefitinib (HR = 2.85; 95% CI: 2.05-3.98; P < 0.0001) (51). However, the final survival data presented recently in the 35th European Society for Medical Oncology (ESMO) congress did not show OS benefit for any of the treatment arms (52). It is worth mentioning that the study was not originally powered to address this point and patients on the chemotherapy arm were allowed to receive EGFR TKI on progression; a point that would confound OS analysis.

In an attempt to confirm that response to EGFR TKI is mutation-specific rather than race-specific, Rosell et al conducted a large prospective screening study in Spain for EGFR mutation in 2105 patients with non squamous NSCLC (53). The results showed that around 16% (350 patients) had an EGFR mutated tumor. It is important to note though that the study population was enriched with women and never-smokers, possibly because physicians were aware that EGFR mutations are more frequent in these subgroups. For the 217 EGFR mutation-positive patients who received treatment with erlotinib (113 as first-line and 104 as second- or third-line therapy), a 71% RR was observed, which is highly comparable to the RR observed in Asian patients with EGFR mutation. Median PFS and OS were 14 and 27 months, respectively; which is by far the longest survival times ever reported in Caucasian patients with advanced NSCLC.

Later studies further demonstrated that EGFR mutations not only predict response to EGFR TKI but also associated with better prognosis. In the CALGB 30406 study; 182 patients (Chemotherapy-naïve, never, or light former smokers and with advanced lung adenocarcinoma) were randomized to erlotinib (150mg/day) or the same drug in combination with carboplatin (AUC 6) and paclitaxel (200mg/m2). Around 39% of patients had EGFR mutation. This group had a significantly better RR (P

< 0.0001 both arms), PFS (P < 0.0001 both arms) and OS (P = 0.0027 E; P = 0.0009 ECP) than EGFR wild type patients (54).

Recently the results of the OPTIMAL study were presented. This is a randomised phase III study which compares erlotinib to the combination of gemcitabine and carboplatin in patients with advanced NSCLC harbouring EGFR exon 19 or 21 mutation. In the intent-to-treat analysis, erlotinib reduced the risk of progression by 84% (P < 0.0001) over gemcitabine/carboplatin. All subgroup analyses heavily favoured erlotinib, with hazard ratios ranging from 0.13 to 0.27. Consistent benefit was observed regardless of histology, smoking history, age, gender, or disease stage. In addition to improvements in PFS, the erlotinib-treated patients also had a significantly higher response rate (83% vs 36%; P < 0.0001) and disease control rate (96% vs 82%; P = 0.002).

The overall survival data are not yet mature. Erlotinib was highly effective regardless of the mutation type as well, though longer PFS was observed in patients with exon 19 deletions. Baseline c-MET amplification status was not predictive of efficacy in either arm. Safety data confirmed the favourable tolerability profile of erlotinib, with a lower incidence of adverse events and serious adverse events vs gemcitabine/carboplatin (55).

It is worth mentioning that a group of patients who harbor the EML4-ALK translocation does not seem to respond to EGFR TKI therapy (56). The prevalence of this translocation in an unselected patient population is estimated to be approximately 5%, but the rate seems to be higher in patients with a history of never or light smoking and EGFR wild-type mutational status (57). Tumors with an EML4-ALK translocation do not seem to respond to EGFR TKI therapy. A single-arm phase II trial of an ALK and c-met inhibitor, crizotinib, in patients with tumors harboring an EML4-ALK translocation has demonstrated a high response rate, disease control rate, and 6-month PFS (58). The future development of this agent will be in patients with a distinct molecular subtype of NSCLC.

## EGFR maintenance therapy

Regarding the role of EGFR TKIs in maintenance therapy, there is a large debate about their activity and their clinical benefit. Erlotinib was tested as a maintenance therapy in a non-selected patient population with NSCLC without progression after four cycles of platinum doublets (SATURN study) (59). 889 patients were randomly assigned to receive either erlotinib or placebo. The trial showed a modest improvement in PFS in favor of maintenance erlotinib (HR = 0.71; 95% CI: 0.62-0.82; P < 0.0001) with no observed differences across histological subtypes. A recent analysis presented in the 35th ESMO congress showed that OS benefit of maintenance therapy was achieved only in those patients who had achieved stable disease (HR = 0.72; 95% CI: 0.59-0.89) following four cycles of chemotherapy compared to those who achieved CR/PR (HR = 0.94; 95% CI: 0.74-1.20) (60).

The west Japan Thoracic Oncology Group carried out a large phase III study with upfront randomization to first-line treatment with either platinum doublet for three cycles followed by gefitinib or continuing the same regimen up to six cycles in non-selected chemo-naïve stage IIIB/IV NSCLC patients. PFS was improved by approximately 10 days with gefitinib (HR = 0.68, 95% CI: 0.57–0.80, P < 0.001), with no difference in overall survival in the intent-to-treat analysis (61). In the EORTC 08021 study that was presented in the last ASCO meeting; patients with advanced NSCLC not-progressing after 4 cycles of platinum-based regimens were randomized to receive either gefitinib 250 mg/day or placebo until progression or unacceptable toxicity. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS) and toxicity. After inclusion of 173 pts, the trial was prematurely closed due to poor accrual. There was improvement in PFS favouring gefitinib (medians 4.1 and 2.9 months, HR = 0.61, 95% CI: 0.45-0.83, P = 0.0015) with no improvement in OS (medians 10.9 and 9.4 months, HR 0.83 [95% CI: 0.60-1.15]; P = 0.2) (62). While these studies were conducted in unselected population, yet based on the available data, maintenance therapy with EGFR TKIs cannot be considered standard at the time being given the modest improvement in PFS without clinically meaningful impact on OS.

## Monoclonal EGFR Antibodies: Cetuximab

Cetuximab is a chimeric monoclonal antibody against the extracellular domain of EGFR with activity in a broad spectrum of tumor types, including lung cancer (63-65).

At least two phase II trials combining cetuximab with paclitaxel/carboplatin produced an overall RR in the range of 25% and PFS in the range of 5-6 months (66,67). Similar results were seen when cetuximab was combined with gemcitabine and carboplatin (68). A randomized phase II study comparing vinorelbine/cisplatin with the same chemotherapy plus cetuximab suggested that addition of cetuximab led to better outcomes (RR 35% vs 28%; median PFS, 5.0 vs 4.6 months; median OS, 8.3 vs 7.3) (69). Similar results were seen in a randomized phase II study combining cetuximab with paclitaxel and carboplatin (70). Based on the promising data from the phase II trials, two phase III trials (BMS-099 and FLEX) were planned, trying to validate the effectiveness of cetuximab in advanced NSCLC. In the BMS-099 trial, 676 patients who had not received prior therapy for metastatic disease were randomized to carboplatin and a taxanes (either paclitaxel or docetaxel at the clinician's discretion) with or without cetuximab

(71). No significant improvement in PFS or OS were observed, although there was a significant improvement in overall RR (25.7% vs 17.2%, P = 0.007).

The second trial (FLEX) assessed another doublet regimen (cisplatin and vinorelbine) with or without cetuximab in patients with immunohistochemical evidence of EGFR expression in their tumors. Among 1,125 patients randomized, median OS was improved in patients who received cetuximab (11.3 vs 10.1 months, P = 0.044) (72). This benefit was selectively observed among patients with squamous histology which stands in contrast to data for other agents in which a selective benefit is observed in those patients with adenocarcinoma. Although the benefit with the addition of cetuximab was modest, the results of this trial led to the incorporation of cetuximab in the National Comprehensive Cancer Network (USA) guidelines for the use in the first line setting in combination with Cisplatin and Vinorelbine.

Given the established role of k-ras in colorectal cancer (73), it has been assessed in NSCLC patients receiving cetuximab as well to examine whether it could function as a predictive marker for cetuximab in NSCLC as well or not. However, correlative analyses accompanying both BMS-099 and FLEX suggest no difference in clinical outcome on the basis of k-ras status (74). In addition to laboratory biomarkers, much interest surrounds the use of skin rash as a predictor of cetuximab efficacy (76). A formal metric to assess rash in relation to cetuximab therapy has been established, termed the EGFR-inhibition related rash (EIRR) rating scale. The scale has been validated prospectively in a trial of cetuximab with pemetrexed in advanced NSCLC, and is being applied in larger patients setting (77).

## Conclusion

The principle of selecting patients most likely to benefit from therapy according to their genetic profile has led to substantial clinical benefit in some tumour types, and has potential to considerably refine treatment in advanced NSCLC. Significant progress has been achieved in using EGFR targeting agents in advanced NSCLC. For EGFR TKI, it is clear that EGFR mutation in exon 19 is highly predictive. This runs in line with earlier clinical data linking response to these agents to non-smoking females of Asian origin, who commonly harbor these mutations. Thus validation for this assay is clearly needed. In our opinion, EGFR TKIs should not be given as first-line treatment in the absence of an EGFR mutation test. For those patients who achieve resistance to EGFR TKI, testing for EML4-ALK translocation could help in identifying a group who could benefit of a met inhibitor and a lot of research in currently ongoing in this area.

The picture is not as clear regarding cetuximab, which is not yet approved in Europe or the US in upfront therapy of advanced NSCLC. Unlike colon cancer, it appears that k-ras status does not predict benefit of cetuximab in this setting and hence still a lot of work is needed in this field.

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