EGFR pathway in advanced non-small cell lung cancer

Valentina Merlo¹, Marina Longo², Silvia Novello², Giorgio Vittorio Scagliotti²

¹Department of Medical Oncology, Santa Maria della Misericordia University Hospital, Udine, Italy, ²Thoracic Oncology Unit, University of Turin, AOU San Luigi Gonzaga-Orbassano (TO), Italy

TABLE OF CONTENTS

1. Abstract
2. Introduction
   2.1. EGFR
3. ERLOTINIB
   3.1. First line therapy
   3.2. Second-third line therapy
   3.3. Maintenance therapy
4. gefitinib
   4.1. First line treatment
      4.1.1. Single agents studies
      4.1.2. First line studies in combination with chemotherapy
   4.2. Second line studies
   4.3. Maintenance therapy
5. Cetuximab
   5.1. First line studies
   5.2. Second line studies
6. Perspectives
7. References

1. ABSTRACT

Chemotherapy is the standard of care for patients with advanced stage non-small cell lung cancer (NSCLC) because of the modest improvement in survival and quality of life but its efficacy has already reached a plateau. Several molecular targets involved in the uncontrolled growth of lung cancer cells has been recently discovered and Epidermal Growth Factor Receptor (EGFR) pathway is as a key therapeutic target. Strategies to block such pathway include tyrosine kinase inhibitors (TKIs) and monoclonal antibodies. Erlotinib and gefitinib are two EGFR-TKI active against NSCLC. Their efficacy has been proven to be definitively superior in presence of activating EGFR mutation in the tumor. This evidence does not apply to the monoclonal antibody cetuximab, which efficacy in NSCLC was recently demonstrated in a single phase III study. The good tolerability profile of EGFR inhibitors make these agents suitable for maintenance and adjuvant setting, while sequencing of EGFR-TKIs and chemotherapy seems to be preferred. This article reviews the role of EGFR inhibitors focusing mainly on compounds in phase III clinical development.

2. INTRODUCTION

Lung cancer is leading cause of cancer related mortality worldwide, accounting for over one million deaths annually. The vast majority of patients present metastatic disease at time of diagnosis, with a 5-year survival rate of approximately 3.5% (1). For these patients the clinical benefit from first line chemotherapy with platinum-based doublets has reached a therapeutic plateau with a median survival time for patients with stage IV disease of approximately 8-10 months (2).

The development of biological agents represents another opportunity in the treatment of advanced non small cell lung cancer (NSCLC) either in combination with cytotoxic drugs or as single agent therapy, both in first or second line setting. Furthermore, on the basis of the established activity of some of these agents in NSCLC coupled with a reasonable toxicity profile, these drugs have been recently considered also for maintenance therapy.

The epidermal growth factor receptor (EGFR) could be considered as one of the most relevant targets for
cancer treatment: growth of human tumours is frequently related to aberrant cellular signalling by inappropriate activation of receptor tyrosine kinase via mutation, over expression or ectopic ligand production (3).

2.1. EGFR

EGFR (Erb-1) is part of the Erb family receptors, which includes HER2/neu (Erb-2), HER-3 (Erb-3) and HER-4 (Erb B4). There are several ligands for EGFR, also including transforming growth factors α (TGFα) and amphiregulin. Ligand binding results in EGFR homodimerization or heterodimerization with other HER/neu family receptors. The activation of EGFR leads to phosphorylation of the intracellular tyrosine kinase domain, with a subsequent activation of the dependant downstream pathway, which include RAS and mitogen activated protein kinase. These signalling pathways are involved in cellular proliferation, motility angiogenesis, invasion and inhibition of apoptosis (4). EGFR is highly over-expressed in a number of human cancers, such as breast, head and neck, NSCLC, and other epithelial cancers (5). In NSCLC, EGFR expression is increased in tumour compared to the normal adjacent lung tissue, as well as the expression levels of TGF-α and other EGFR ligands (5, 6).

Experimental data indicate the oncogenic potential of EGFR mutations: for instance, the L858R mutation in exon 21, the G719S mutation in exon 18 and the insertion in exon 20 confer ligand independent cellular transformation (7). The L858R mutation in exon 21 and a deletion of a conserved sequence in exon 19 represent the most commonly observed EGFR mutations.

Agents acting against EGFR are currently classified in two categories: those directed against the external domain of the EGFR such as cetuximab and panitumumab and those blocking the activity of the intracellular tyrosine kinase portion of the receptor such as erlotinib and gefitinib.

Prospective and retrospective trials confirmed that the response rate to tyrosine kinase inhibitors (TKIs) in patients with EGFR mutation is up to 80% and patients with EGFR-mutated tumours have significantly longer survival than those with EGFR-wild-type tumours (8, 9).

3. ERLOTINIB

Erlotinib reversibly binds to the ATP-binding site and inhibits autophosphorylation by EGFR TK, resulting in a blockage of downstream EGFR signal transduction pathways. Its bioavailability significantly depends from food administration: with food intake there is an increase in mean AUC up to 33%, which translates into an increase of the drug related risk side effects. Furthermore pharmacokinetic data indicate a difference in drug exposure between current and never smokers with a maximum tolerated dose (MTD) of erlotinib of 300 mg in current smokers compared with 150 mg as a result of a phase I trial for all comers (10, 11).

3.1. First line therapy

Erlotinib as a single agent has been shown clinically meaningful and statistically significant overall survival benefit over placebo in advanced NSCLC patients who have failed previous chemotherapy and these data led to the registration of erlotinib as second/third line treatment for NSCLC in USA, Europe and Japan (12).

In two large randomised phase III trials the addition of erlotinib to standard chemotherapy failed to demonstrated an improvement in survival in first line treatment (13, 14). Despite these results on the overall population, subset analyses demonstrated an overall survival advantage in never smoker patients treated with erlotinib plus chemotherapy compared with never smokers treated with placeo plus chemotherapy (22.5 versus 10.1 months; HR=0.49, 95% CI 0.28-0.85).

The reason why the addition of EGFR TKI to chemotherapy in first line setting for advanced NSCLC leads to therapeutic failure is unknown but preclinical data indicate that EGFR-TKI induces G1 cell cycle arrest, which might interfere with cytotoxic therapy (15). Based on this hypothesis, two studies have been initiated with sequential or intermittent dosing schedules.

The FAST-ACT is a randomised phase II trial, in which patients with untreated, advanced NSCLC received cisplatin and gemcitabine every four weeks, with either erlotinib or placebo from day 15 to 28 of each cycle. Preliminary results revealed a significant progression free survival advantage for experimental arm (7.3 versus 5.5 months), but no data are available for OS. Overall safety profiles were similar between the two arms (16).

A phase I study of erlotinib and pemetrexed in chemonäive patients with advanced NSCLC tested an intermittent dose schedule and pemetrexed was administered every 21 days together with erlotinib continuously or two different schedules (weekly on day 2, 9 and 16 or daily from day 2 until day 16). Dose limiting toxic effects were not experienced up to erlotinib 150 mg/day plus pemetrexed 600 mg/mq and concurrent administrations did not affect pharmacokinetics parameters. Among twenty patients two achieved partial response and nine had stable disease (17). Other phase II studies in first line setting, using the sequential/intermittent schedule failed to demonstrated a significant improvement in survival (15).

Other trials in first line setting have investigated the role of erlotinib as monotherapy in enriched population (e.g. female, never smokers or elderly and poor performance status patients).

A phase II study examined the efficacy of erlotinib in a group of 40 chemotherapy-naïve female, non smoker patients with adenocarcinoma histology: the progression free survival (PFS) was equal to 5.6 months and the overall survival at the time of reporting exceeds 23 months (18).

In another trial, chemonäive NSCLC patients with ECOG-PS 2 were randomised to receive erlotinib or carboplatin/paclitaxel. Patients treated with erlotinib had a
worse progression-free survival (PFS) (1.9 versus 3.5 months, \( p=0.06 \)) and overall survival (OS) (6.5 versus 9.7 months, \( p=0.018 \)) compared to those treated with chemotherapy (19).

Elderly patients with NSCLC benefit from treatment with chemotherapy, but with an increased risk for toxicity. A phase II study was conducted to evaluate the efficacy and tolerability of erlotinib in previously untreated patients aged 70 years or older. The clinical benefit rate was 52\% with a median survival time equal to 11 months. The predominant adverse events were acneiform rash and diarrhoea, but overall toxicity was manageable, suggesting erlotinib as a first line reasonable option for elderly population (20).

However, a phase III trial in elderly patients with advanced NSCLC presented at 2010 American Society of Clinical Oncology (ASCO) annual meeting, which compared carboplatin/vinorelbine (CV) versus erlotinib in the first line setting failed to demonstrated a superiority of the molecular targeted agent. In 284 patients PFS was in favour of CV (median PFS 2.4 versus 4.6 months; HR 1.6) as well as response rate (RR) (7.8 versus 28.3\%; \( p=0.0001 \)), while no difference in overall survival (OS) appeared (7.3 versus 8.4 months; HR 1.24) (21).

In the phase III OPTIMAL trial chemo naïve NSCLC patients with EGFR exon 19 or L858R mutations were eligible and randomised to receive erlotinib 150 mg/die up to progression or gemcitabine and carboplatin up to 4 cycles. Among 549 patients screened, 186 were positive to have EGFR mutations (34.3\%). With the exception of diarrhoea, skin rash and retinal detachment (reported with a percentage equal to 1.2 \% each, grade 3-4) all the other grade 3-4 toxicities were more frequent in the chemotherapy arm (22).

The CALGB 30406 randomised phase II trial evaluated erlotinib versus six cycles of carboplatin and paclitaxel plus erlotinib in chemosensitive stage IIIIB/IV adenocarcinoma or BAC patients who were never or light former smokers. In 181 patients no significant difference was seen in terms of PFS or OS, but, analysing EGFR mutated tumors only, there was a benefit in terms of RR, PFS and OS from erlotinib and also from erlotinib plus chemotherapy (23).

These data support the concept that EGFR-TKIs alone are an acceptable first line therapy for advanced NSCLC patients with tumours harbouring EGFR mutations.

On the basis of its easily administration and good tolerability erlotinib has been also evaluated in poor performance status (PS) patients. Six hundred seventy chemo naïve patients with PS 2-3 or with impaired renal function were randomised to receive erlotinib 150 mg/day or placebo. In the overall population no differences were detected between the two arms in terms of OS (3.8 versus 3.6 months in the erlotinib and the placebo arm, respectively) or PFS (2.8 versus 2.7 months). However erlotinib improved OS in females, with 26\% reduction in death rate (HR=0.74; \( p=0.025 \)), despite the low EGFR mutation rate across the overall population (3.5\%) receiving erlotinib and with a benefit also present in EGFR wild type females (42\% reduction in PFS; HR=0.58, \( p=0.009 \)) (24).

Because erlotinib alone was perceived as a valid alternative to chemotherapy in unselected NSCLC patients, the TORCH trial evaluated a first line treatment with erlotinib followed by second line double chemotherapy versus first line cisplatin and gemcitabine followed by erlotinib as a second line therapy (25, 20, 27). Seven hundred sixty patients were randomised and the primary end point of improving OS was not met: the median survival was 12 months in the chemotheraphy first line followed by erlotinib arm versus 8.5 months in the erlotinib followed by chemotherapy arm (HR=1.36; \( p=0.002 \)) (27). Retrospective and prospective data underline the relevance of EGFR mutation as independent predictor of response, PFS and OS in patients with NSCLC treated with erlotinib. A screening study for EGFR mutations in more than 2000 patients with NSCLC reported a mutation rate equal to 16.6\% and no significant difference in PFS and OS according to first line versus second or third line therapy (27).

### 3.2. Second-third line therapy

The BR.21 landmark phase III trial established the role of Erlotinib in second-third line setting: 731 previously treated patients with advanced NSCLC were randomised in a 2:1 ratio to receive erlotinib or placebo. The response rate and the overall survival were 8.9 \% and 1\% and 6.7 months and 4.7 months (\( P=0.001 \)) in the erlotinib and in the placebo arm, respectively (12).

More patients in the erlotinib arm experienced symptom improvement. The major toxicities were acneiform rash and diarrhoea, though grade 3 to 4 toxicity occurred in less than 10\% of patients.

This led to approval of erlotinib by Food and Drug Administration (FDA) on November 2004 for treatment of patients with locally advanced or metastatic NSCLC after failure of at least one previous chemotherapy regimen (12).

The benefit of erlotinib was demonstrated in all the analysed subgroups. However the advantage was more pronounced among Asiatic patients, never smokers, females and patients with a pathologic diagnosis of adenocarcinoma.

In light of the proven role of erlotinib in second line, of the positive effect of adding bevacizumab to chemotherapy in first line NSCLC and of the positive results of a phase II study the Beta Lung trial aimed to demonstrate the effect of the addition of bevacizumab (B) to erlotinib (E) in previously treated with advanced non-squamous NSCLC patients. Despite some preliminary positive results in terms of PFS (BE 3.3 months versus 1.7 months; HR 0.62) and RR (12.6\% BE versus 6.2\% E;
EGFR pathway in advanced NSCLC

p=0.006), the primary end point of OS was not met (28, 29).

Preclinical data demonstrated that the addition of pemetrexed to erlotinib sensitizing erlotinib-resistant cells to both agents and leads to maximal synergistic cytotoxicity comparable to erlotinib-sensitive NSCLC cells. A phase II trial was designed to determine whether pharmacodynamic separation of erlotinib and pemetrexed improves clinical efficacy as compared to that of pemetrexed monotherapy in patients with relapsed or recurrent NSCLC. With a 2:1 randomization design 75 patients were assigned to pemetrexed alone or pemetrexed plus erlotinib 150 mg/day from day 2 to 17 every 21 days. The trial is still recruiting patients with some preliminary positive data in the combination arm (30)

3.3. Maintenance therapy

In advanced NSCLC a theoretical opportunity to improve the outcome is represented by the administration of a maintenance treatment to keep disease control achieved with the standard first line chemotherapy.

Several strategies have been tested including continuation of therapy (prolongation of first line treatment), early second line (administration of an approved agent immediately after completion of first line), and true maintenance (prolonged administration of one of the agents included as part of the first line regimen). On the basis of its good tolerability and the oral administration, erlotinib became one ideal candidate for early second line therapy. In addition data from the phase III front line studies, TRIBUTE and TALENT, which investigated erlotinib in combination with chemotherapy suggested that erlotinib therapy may be effective as maintenance monotherapy after platinum-based treatment (13, 14).

In the TRIBUTE study, among the 861 patients surviving beyond 4 months (408 and 453 patients randomised to erlotinib and placebo, respectively), the median OS with erlotinib was 13.6 months versus 12.2 months in the placebo arm and, among those 740 patients surviving beyond 6 months, median survival with erlotinib was 15.4 versus 13.8 months in the placebo arm.

The SATURN (Sequential Tarceva in Unresectable Lung Cancer) phase 3 trial was planned to evaluate the efficacy of erlotinib as early second therapy in advanced NSCLC.

In this multicentre, double-blind study, patients with advanced NSCLC were randomised to receive either erlotinib or placebo, after documented disease control (objective response plus disease stabilization) achieved with 4 cycles of standard platinum-based doublets. The primary end-point was the PFS, the co-primary endpoint was to determine whether erlotinib administration results in improved progression free survival compared with placebo in patients with EGFR protein expression positivity at immunohistochemistry. Secondary end-point includes OS in the overall population and in patients who were EGFR protein expression positive. Progression free survival was significantly longer in the erlotinib arm (HR=0.71, 95% CI 0.62-0.82; p<0.0001) and clinical benefit was seen irrespective of race, histology or smoking status, even if a clear greater benefit was demonstrated in EGFR mutated patients (EGFR mutational status was available in a small percentage of the population) (31). The advantage was seen in the overall population also in terms of OS, with 12 versus 11 months (HR 0.81, 95% CI 0.70-0.95; p=0.0085) and this benefit was present also in EGFR IHC positive population (HR=0.77, 0.64-0.93; p=0.0063) as well as in patients whose tumours did not harbour activating EGFR mutation (HR=0.77, 0.61-0.97; p=0.0243). Patients achieving a stable disease after first line chemotherapy seemed to have a more pronounced overall survival benefit with maintenance erlotinib compared to the responders (11.9 versus 9.6 months, HR=0.72 for SD; 12.5 versus 12 months; HR=0.94 for responders) (32).

These data led the European Regulatory Agency (EMEA) to endorse the registration of erlotinib in maintenance setting in those patients reaching a stabilization after a standard induction therapy.

The ATLAS trial was designed to evaluate the benefit of the addition of erlotinib to bevacizumab versus bevacizumab alone as a maintenance therapy after an induction with a platinum-based chemotherapy plus bevacizumab. The trial met the primary end point of improving PFS but this improvement was modest if: 4.76 months versus 3.75 months (HR=0.72, p=0.0012) (33). However, no statistically significant benefit was shown for OS: 15.9 months versus 13.9 months (HR=0.9, p=0.2686) (34).

4. GEFITINIB

Gefitinib has been extensively investigated in NSCLC, having an intriguing clinical development process. In initial phase II dose finding trials gefitinib showed activity as monotherapy in previously treated NSCLC patients, with response rates ranging between 10% to 20% and with benefit in symptom relief (35, 36). In May 2003, these promising results led to the expedited approval by the FDA as third-line therapy for advanced NSCLC after prior platinum and docetaxel-based chemotherapy. However, the post-approval phase III placebo-controlled study, the Iressa Survival Evaluation in Lung Cancer (ISEL) trial resulted to be negative, showing only a trend in favour of the experimental arm in terms of overall survival (5.6 versus 5.1 months, p = .087) (37). As a consequence, in June 2005, the FDA revised the indication limited the use of gefitinib only in patients treated at that time and with benefit from this agent or that were included in clinical trials. Only in July 2009, based on the positive results of two large phase III trials (the INTEREST trial, comparing gefitinib versus docetaxel in previously treated NSCLC patients, with the IPASS trial, that randomized chemo-naïve, clinically selected NSCLC patients to first-line gefitinib versus carboplatin and paclitaxel), gefitinib was approved by the EMEA for the treatment of both chemo-naïve and pre-treated patients, with locally advanced or metastatic NSCLC and EGFR activating mutations (38, 39).
EGFR pathway in advanced NSCLC

4.1. First line treatment

4.1.1. Single agent studies

The role of gefitinib as an alternative to chemotherapy was investigated both in first and second-line setting. Mild toxicity and an advantage in terms of quality of life were expected, based on the results of previous studies.

The Iressa Pan-Asia Study (IPASS) was a phase III trial, which was designed to demonstrate a non-inferiority in PFS for gefitinib versus paclitaxel and carboplatin. A non-inferiority margin was defined by a hazard ratio (HR) with an upper limit equal to 1.2 for gefitinib, compared to chemotherapy. Eligible patients were non-smokers or former light smokers (< 10 pack years), pathologically confirmed stage IIIIB or IV NSCLC with histological features of adenocarcinoma and a performance status of 0–2; no selection was performed based on tumour molecular profiles, but patients were assessed for the EGFR mutations status, whenever possible. Gefitinib demonstrated superior efficacy compared to carboplatin-paclitaxel (HR for PFS 0.74; CI 0.65-0.85; p=0.0001). Median PFS was similar in the two arms (5.7 versus 5.8 months for gefitinib and chemotherapy, respectively) showing a better outcome with chemotherapy in the first 6 months, but favouring subsequently gefitinib. The EGFR-TKI agent was associated with a higher RR in the overall population (43% versus 32.2%, p<0.001), a more favourable toxicity profile, a better quality of life and similar symptom improvement rates. A subgroup analysis of patients with evaluable EGFR mutations status (N=437, EGFR mutation positive: N=261) showed significant PFS benefit in EGFR mutation-positive patients treated with gefitinib (HR 0.48; 95% CI 0.36-0.64; p=0.0001), whereas chemotherapy provided significantly better outcomes in the mutation-negative subgroup (HR 2.85; CI 2.05-3.98; p<0.0001). The ORR also favoured gefitinib in the mutation-positive subgroup (71.2% versus 47.3%; p<0.0001), instead these results do not apply to the mutation-negative subgroup (RR: 1.1% versus 23.5%, p = 0.001). OS data are still pending: a preliminary analysis according to the mutational status has shown no difference between the two arms (39, 40).

In the phase III randomised FIRST-SIGNAL trial, 313 advanced, never smoker patients, with adenocarcinoma were treated with gefitinib or cisplatin and gemcitabine. While similar results were seen between the two arms in terms of OS (21.3 months versus 23.3 months in the gefitinib and chemotherapy arm, respectively; HR=1.003), there was an advantage in terms of PFS favouring gefitinib in those patients with EGFR mutation positive tumours and chemotherapy in mutation negative tumours. (41).

The NEJ 002 Japanese study was the first prospective study evaluating first line gefitinib versus chemotherapy in a molecularly selected population of EGFR mutation-positive patients. After inclusion of 200 patients a pre-planned interim analysis showed a significant PFS benefit favouring gefitinib over carboplatin and paclitaxel (median PFS 10.4 vs. 5.5 months, respectively; HR 0.357 [95% CI 0.25–0.51; p < 0.001]). The study was then early terminated as indicated by the Independent Data Monitoring Committee of the study (42).

A post-hoc analysis of the efficacy in patients receiving full dose of gefitinib or a dose reduction at any point of treatment revealed that low dose gefitinib (mostly an every-2-days schedule) may be clinically not inferior to standard schedule for NSCLC patients with EGFR mutations (43).

Similarly, a recent phase III Japanese trial, randomly assigned 177 chemotherapy-naïve patients with advanced NSCLC and sensitizing EGFR mutations to receive either gefitinib or cisplatin plus docetaxel as first-line treatment. The gefitinib group showed a statistically significant superiority in terms of PFS (9.2 vs. 6.3 months; HR 0.489; 95% CI 0.336 – 0.710; p < 0.0001) and disease control rate (93.1 versus 78%; 95% CI 2.7 – 27.6; p=0.020). OS data are not yet available (44).

Phase II trials of first line gefitinib in elderly patients with advanced NSCLC were also performed. Among 57 chemonaïve patients aged 70 years or older, those EGFR mutations positive (38%) were treated with gefitinib 250 mg/day, while patients without mutations received vinorelbine 25 mg/m² days 1 and 8, every 21 days or gemcitabine 1000 mg/m² on days 1 and 8, every 21 days with RR as primary end point. Customized gefitinib in elderly patients resulted in remarkable response to EGFR-TKI with a RR of 45% (versus 19% in those treated with chemotherapy) and median OS of 24.4 months (versus 18.9 months in patients receiving monochemotherapy) (45).

In the NEJ003 phase II study, patients with advanced NSCLC 75 years old or more with EGFR mutations, received gefitinib 250 mg/day. The overall RR was equal to 74%, with a disease control rate of 90% and PFS of 13.6 months (46).

4.1.2. First line studies in combination with chemotherapy

The favourable tolerability profile of gefitinib as observed in phase II trials, coupled with its mechanism of action, which is distinct from that of cytotoxic agents, provided the rationale for the use of gefitinib in combination with standard cytotoxic regimens. This rationale was also supported by in vitro and in vivo preclinical data which showed a synergistic effect of gefitinib with several cytotoxic drugs against different human solid tumour types (47, 48). Interestingly, synergy was observed in the combination of gefitinib and cisplatin while, for instance, no synergic activity was seen between gemcitabine and gefitinib. No clinically significant pharmacokinetic interactions and a good tolerability profile were reported for the combination of gefitinib with carboplatin and paclitaxel (49). Pharmacokinetic data have identified two doses of gefitinib worth of further investigation: the lowest dose of 250 mg/day, which is just above the lowest dose associated with clinical response and the 300 mg/daily dose, representing the maximum tolerated dose for this agent (50, 51, 52, 53).
EGFR pathway in advanced NSCLC

In 2004 the results of The Iressa NSCLC Trial Assessing Combination Treatment (INTACT) 1 and 2, conducted mainly in Europe and in the United States, respectively, were published. These two multicenter randomized, placebo-controlled studies evaluated the combination of gefitinib 250 or 500 mg/day with gemcitabine plus cisplatin or paclitaxel and carboplatin, respectively, as first-line treatment of advanced NSCLC patients. A maximum of six cycles of chemotherapy plus gefitinib were planned, followed by maintenance gefitinib or placebo until disease progression or drug intolerance. In both trials, the addition of gefitinib to chemotherapy failed to demonstrate any significant benefit in terms of response rate, progression-free and overall survival (54, 55).

4.2. Second line studies

The phase II IRESSA Dose Evaluation in Advanced Lung Cancer 1 and 2 trials (IDEAL-1 and 2) were designed to evaluate the activity and safety of gefitinib in NSCLC patients who had previously received one or two chemotherapy regimens, at least one of which containing platinum.

These multicenter, randomized, double-blind, trials compared gefitinib 250 mg/daily versus 500 mg/daily. For IDEAL-1 about 200 patients were enrolled in Japan, Europe, South Africa and Australia, while for IDEAL-2 approximately the same number of patients was enrolled in the United States.

In these two trials, response rates were similar with both doses: 18% and 12% in the 250 mg groups versus 19% and 9% in the 500 mg groups, respectively and no major differences were seen in terms of OS (7.6 and 6.1 months versus 8.0 and 6.0 months, respectively).

Most drug-related adverse events were mild and non-cumulative. The 250 mg/daily dose was better tolerated than the 500 mg/daily dose (the frequency of grade 3/4 drug-related adverse events was 1.5% and 4.7% in the 250 mg and 500 mg dose levels, respectively). In both studies, improvements in disease-related symptoms and quality-of-life were associated with objective tumour response, progression-free and overall survival (35, 36).

The phase III IRESSA Survival Evaluation in Advanced Lung Cancer (ISEL) trial represented the follow-up study in which gefitinib was compared to placebo, in previously treated NSCLC patients. Despite a significantly higher objective response rate in the experimental arm (8% vs 1%, p < 0.0001), no significant difference was seen between the two groups in the overall population (5.6 vs 5.1 months) and in the adenocarcinoma subset (6.3 vs 5.4 months). However, a pre-planned sub-analysis demonstrated a statistically significant survival benefit for gefitinib compared with placebo in Asian population (median survival, 9.5 vs 5.5 months; HR 0.66; 95%CI 0.48-0.91; p = 0.01), as well as in never smokers (median survival, 8.9 vs. 6.1 months; HR 0.67; 95%CI 0.49-0.92; p =0.012) (37). In the group of all Asian patients from the ISEL trial, a significantly longer survival was observed in the gefitinib group for female, adenocarcinoma and never smokers (56).

More recently, gefitinib has been compared with docetaxel in the second line setting. In the phase II, randomized Second-line Indication for Gefitinib in NSCLC (SIGN) trial, gefitinib was better tolerated than docetaxel with grade 3-4 toxic effects observed in 9% of the patients receiving the EGFR-TKI versus 25% of those allocated to single agent chemotherapy. Response and survival outcomes were similar in the two arms, although the trial was not powered to demonstrate any survival difference (57). Similar results were also seen in the Japanese, phase III V-15-32 trial, which failed to demonstrate a non-inferiority of gefitinib versus docetaxel in terms of overall survival (58).

The INTEREST trial was a multicenter, open-label, phase III study, which randomized 1466 patients to gefitinib or docetaxel. The study demonstrated the non-inferiority of gefitinib in terms of OS (593 versus 576 events; HR 1.020, 95% CI 0.905 - 1.150), with similar PFS outcomes (HR 1.04, 95% CI 0.93–1.18; p=0.47) and RR (9.1% versus 7.6%; OR 1.22, 95% CI 0.82–1.84; p=0.33) (59). In this trial neither clinical characteristics that are associated with a higher frequency of EGFR-mutations (Asian origin, female gender, history of never or light smoking, adenocarcinoma histology) nor molecular features (EGFR or KRAS mutational status, EGFR protein expression, EGFR gene copy number) were unable to identify subgroups of patients, who definitely did not benefit from treatment with gefitinib (60).

More recently a meta-analysis of four randomized trials of gefitinib versus docetaxel (INTEREST, V-15-32, ISTANA, SIGN) has confirmed that gefitinib yields at least comparable efficacy to that obtained with single agent chemotherapy (61).

Similarly to the results obtained with erlotinib in EGFR-mutated tumours (see above) in a combined survival analyses of seven prospective trials with gefitinib in Japanese patients a total of 148 NSCLC with EGFR mutations were considered. The overall response rate to gefitinib was 76.4%. The median PFS and OS were 9.7 months and 24.3 months, respectively. Of the 148 patients, 87 received gefitinib as a first-line therapy, whereas 61 received systemic chemotherapy before gefitinib treatment. The median PFS after the start of first-line therapy was significantly longer in the gefitinib-first group than in the chemotherapy-first group (10.7 versus 6.0 months; P < 0.001), whereas no significant difference in median OS was apparent between the two groups (27.7 versus 25.7 months; P = 0.782)(62).

A randomized phase II trial comparing gefitinib versus erlotinib in 96 patients with advanced NSCLC, who failed after first line treatment did not show any statistically significant difference in RR, PFS, quality of life improvements or tolerability (63).

4.3. Maintenance therapy

The oral administration and its mild toxicity profile makes gefitinib an ideal agent to be potentially evaluated in the maintenance setting.
EGFR pathway in advanced NSCLC

In the SWOG 0023 trial, stage III NSCLC patients received cisplatin plus etoposide with concurrent thoracic radiation therapy, followed by consolidation docetaxel. Non-progressing patients were randomly assigned to gefitinib or placebo until disease progression, intolerable toxicity, or for a maximum of 5 years. The study was closed prematurely and gefitinib maintenance failed to show any survival advantage. In fact, patients who completed consolidation therapy and were assigned to the experimental arm showed an unexpectedly worse outcome with a median survival of 23 versus 35 months in the gefitinib and placebo arm, respectively (p = 0.013). The detrimental effect of gefitinib could not be related with the toxicity profile, having a toxic death rate of 2% versus 0% in the two arms, respectively (64).

The EORTC randomized, placebo-controlled phase III trial 08021 evaluated the role of gefitinib administered to NSCLC not progressing patients following 4 cycles of platinum-based chemotherapy. The study was prematurely closed to entry due to low accrual (173 patients included versus a planned 598 patients) and no differences in OS could be detected, but the continuous administration of gefitinib was well tolerated and a significant PFS benefit in favour of gefitinib was observed (4.1 versus 2.9 months, HR 0.61, 95% CI 0.45 – 0.83; p=0.0015) (65).

Consolidation therapy is defined as the prolongation of the induction treatment using one of the agent started upfront for a well established time and/or number of cycles. In this perspective, the INTACT 1 and 2 studies, which were discussed above, may be considered as a sort of consolidation therapy studies, in which the oral EGFR TKI treatment was administered until disease progression. Despite the negative results of these trials, it should be noted that in the INTACT 2 trial there was a trend toward improved survival in the subset of patients with adenocarcinoma histology, who had received chemotherapy for ≥ 90 days in the gefitinib 250 mg per day arm (median survival of 17.1 months in the gefitinib arm vs. 13.6 months in the placebo arm; p = 0.05). These data might suggest a possible effect of gefitinib as cytostatic agent, able to maintain tumor regression after chemotherapy (54, 55).

The WJTOG0203 is a recently published consolidation/maintenance therapy trial. Chemonaïve, advanced NSCLC patients (N = 604) were randomly assigned to receive either platinum doublet chemotherapy up to 6 cycles or 3 cycles of a platinum doublet, followed by maintenance gefitinib. Overall survival results did not reach the statistical significance, but a subgroup analysis revealed that adenocarcinoma patients allocated to gefitinib had better outcomes than those treated with exclusive chemotherapy. Besides, a significant PFS benefit was seen in the gefitinib arm (66).

5. CETUXIMAB

5.1. First line studies

Cetuximab has shown efficacy as single agent in metastatic colorectal cancer patients, but more clinically relevant efficacy has been observed when cetuximab has been combined with other treatment modalities, such as radiotherapy or platinum-based therapy in squamous cell cancer of head and neck and irinotecan or oxaliplatin-based chemotherapy in metastatic colorectal cancer (67, 68, 69, 70, 71, 72).

Cetuximab has been also extensively studied in the treatment of advanced NSCLC. Even if the single agent activity of cetuximab in NSCLC appears to be modest, several trials have shown activity in combination with a variety of first-line platinum doublets (73, 74, 75, 76, 77, 78). The randomized phase II trial by Rosell et al., comparing vinorelbine and cisplatin with or without cetuximab in EGFR-expressing NSCLC, demonstrated the safety of the combination. This trial also showed a positive trend toward an improvement in response rate, PFS, and OS (78).

Phase II data led to the development of the FLEX trial, a large phase III study comparing first-line vinorelbine and cisplatin with or without cetuximab, until disease progression or unacceptable toxicity. Eligible patients had EGFR positive tumours as tested by immunohistochemistry, with a performance status of 0-2. No restrictions were performed based on histological features. No difference in PFS between the two treatment arms was noted. However, cetuximab was associated with a statistically significant higher response rate and a modest improvement in OS (1.2-month improvement in median survival; HR for death 0.871; 95% CI 0.762–0.996; p = 0.044). More common drugs-related adverse events in the cetuximab arm included a statistically significant higher rate of grade 3/4 acne-like rash (10% vs <1%), diarrhoea (5% vs. 2%), infusion related reactions (4% vs <1%) and febrile neutropenia (22% vs 15%). The rate of treatment related deaths on the cetuximab and control arm were similar (3% and 2%, respectively) (79).

Subgroup analysis showed no significant interaction between treatment efficacy and patient characteristics (age, sex, performance status, tumour histology, tumour stage, history of smoking). Nevertheless a correlation between the treatment and the ethnic origin was demonstrated, showing a trend of greater efficacy for the addition of cetuximab in Caucasian patients, compared to Asian or other origin. No significant association were found between KRAS mutation status and EGFR gene copy number and the efficacy parameters (80). The only predictor of clinical benefit for the addition of cetuximab to chemotherapy appeared to be treatment-related early acne-like skin rash: OS for those patients receiving cetuximab, who experienced any grade of rash within 3 weeks of treatment initiation was significantly superior (HR = 0.63; p < 0.001) (81).

A second phase III trial of carboplatin and taxane therapy (either paclitaxel or docetaxel at the investigator’s discretion) with or without cetuximab was designed as a supportive trial to the FLEX study. PFS was the primary endpoint and there was no selection of the patients (N=676) on the basis of EGFR expression. There are some similarities with the FLEX trial: both studies showed a statistically significant benefit in ORR with the addition of cetuximab to chemotherapy and failed to show any
significant improvement in PFS. This trial was not sufficiently powered to detect a difference in survival and no significant improvement in OS was seen. However, the magnitude of the HR for death was similar in both studies (0.890 vs 0.871, in FLEX and BMS099 trial, respectively) (82). As in the FLEX trial, no significant correlations were found between KRAS and EGFR mutations, EGFR protein expression and EGFR gene copy number and efficacy parameters (83).

A pooled meta-analysis recently published considered the results of these two phase III trials and those of two randomized phase II trials (73, 75) and a total of 2018 patients were analyzed. The meta-analysis showed the benefit of cetuximab when added to standard first-line platinum-based chemotherapy both in terms of OS (p = 0.010), PFS (p = 0.036) and ORR (p < 0.001) compared to chemotherapy alone (84).

However, these data were not considered robust enough from regulatory agencies and cetuximab is currently not approved for the treatment of advanced NSCLC and only NSCLC patients treated within clinical trials should receive cetuximab.

Interestingly a RR of nearly 50% without a substantial increase in toxicity was recently reported in a phase II trial in which cetuximab was administered with the combination of docetaxel and carboplatin in chemo-naïve patients with advanced NSCLC (85).

The activity of cetuximab in combination with chemotherapy in the front line treatment of NSCLC contrast with the lack of activity of EGFR TKIs following a similar study design. The differences in clinical activity may be due to the different mode of action of these two therapeutic classes. Also, the antibody can down regulate cell surface receptors and mediate immune effects.

To date, identification of biomarkers to predict patient response to therapy remains a critical issue for cetuximab in NSCLC. As mentioned above early-onset acneiform rash may be related to efficacy in patients treated with cetuximab and first-cycle rash efficacy results by histology seem to be highly pronounced for adenocarcinoma and squamous cell carcinomas (81). However intriguing, the role and clinical utility of this surrogate marker remains unclear, and further studies are expected to investigate to what extent EGFR expression and other molecular determinants influence cetuximab activity.

A systematic review of candidate predictive biomarkers was conducted retrospectively on data from studies with cetuximab plus chemotherapy, but no predictive factor for cetuximab benefit was identified. Efficacy of cetuximab was observed regardless of K-ras mutational status or EGFR mutational status (86).

5.2. Second line studies

Phase II trials were conducted evaluating the role of cetuximab in the treatment of pre-treated patients with advanced NSCLC.

A single arm study investigated the efficacy of single agent cetuximab in patients with recurrent or progressive NSCLC, after receiving at least one prior platinum-based chemotherapy regimen. Sixty-six heavily pre-treated patients (58% with ≥2 prior regimens) were assessed for EGFR expression and received weekly cetuximab until disease progression or intolerable toxicities. The results of this phase II trial indicate that single agent cetuximab has modest activity (RR of 4.5% in the overall population and 5% in the EGFR positive population), lower than what usually expected with historical controls. The median time to progression and OS were of 2.3 and 8.9 months, respectively (74). A clinical trial tested the activity of cetuximab in combination with docetaxel in chemotherapy refractory and resistant NSCLC, EGFR positive tumours as tested by immunohistochemistry, in patients with performance status of 0-2. A total of fifty-five patients received the combination until evidence of disease progression or unacceptable toxicity. Docetaxel plus cetuximab showed interesting RR (20%), PFS (2.7 months; 95% CI 1.8-4.4 months) and OS (7.5 months; 95% CI 6.7-12 months) compared with historical control. There was no evidence of additional toxicity resulting from the combination, even if about 80% of patients reported a grade 3 or 4 adverse event. Pharmacokinetics data revealed no differences in the parameters of the chemotherapy agent either alone or in combination with the EGFR inhibitor (87).

These observations have laid the groundwork for the SELECT trial, an ongoing, open-label, randomized, phase III study in patients with recurrent or progressive NSCLC after failure of an initial platinum-based chemotherapy. This four-arm trial is comparing docetaxel and pemetrexed with and without cetuximab: results will be available in the near future.

In addition, there are ongoing trials exploring the combination of cetuximab with gefitinib and erlotinib in patients with refractory NSCLC. In a recent phase II trial, the combined EGFR inhibition with cetuximab and erlotinib administered to metastatic lung adenocarcinoma patients with acquired resistance to erlotinib show no significant activity (88).

6. PERSPECTIVES

We classify a patient as “resistant” when initially refractory to EGFR-TKI treatment or when after an initial, but not lasting response to these agents becomes insensitive (“acquired resistance”). Activating EGFR mutations may predict treatment benefit from EGFR TKIs and different described EGFR mutations are associated with acquired resistance. The T790M mutation is present in 50% of EGFR TKI resistant tumours, mostly detectable before EGFR-TKI treatment (89, 90, 91). Other secondary EGFR point mutations are associated with resistance development, such D761Y. K-ras mutation is associated with poor response to EGFR-TKIs as well as the amplification of pro-oncogene MET (90, 92, 93, 94). To address the issue of resistance of EGFR TKIs, many new agents are currently under investigation in NSCLC. The
### Table 1. BIBW development in non small cell lung cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Design</th>
<th>Line</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lux-Lung 1</td>
<td>IIb/III</td>
<td>BIBW 2992 50mg/daily+BSC 2:1 versus placebo+BSC</td>
<td>II or III</td>
<td>Adenocarcinaoma PD after 1 or 2 line PD after EGFR TKI &gt; 12 weeks ECOG 0-2</td>
</tr>
<tr>
<td>Lux-Lung 2</td>
<td>II</td>
<td>BIBW 2992 50-40 mg/daily</td>
<td>II</td>
<td>Adenocarcinaoma No prior EGFR TKI EGFRm+ ECOG 0-2</td>
</tr>
<tr>
<td>Lux-Lung 3</td>
<td>III</td>
<td>BIBW 2992 40mg/daily 2:1 versus Cisplatin Pemetrexed</td>
<td>I</td>
<td>Adenocarcinaoma EGFRm+ ECOG 0-1</td>
</tr>
<tr>
<td>Lux-Lung 4</td>
<td>I/II</td>
<td>BIBW 2992 50 mg/daily</td>
<td>II - III or more</td>
<td>Japanese pts Phase I: NSCLC, conventional treatment failure ECOG 0-1 BIBW 20 mg→ 30 mg→ 40 mg→ 50 mg until DLT Phase II: Adenocarcinaoma PD after 1 or 2 lines CT PD after 1 line EGFR TKI ECOG 0-1 BIBW 20 mg→ 50 mg→ 40 mg→ 30 mg until DLT</td>
</tr>
<tr>
<td>Lux-Lung 5</td>
<td>III</td>
<td>BIBW 2992 50 mg/daily plus weekly Paclitaxel versus investigator’s choice of CT following BIBW 2992 monotherapy 2:1</td>
<td>II or III</td>
<td>Adenocarcinaoma PD after 1 lines CT PD after 1 line EGFR TKI ECOG 0-2</td>
</tr>
<tr>
<td>Lux-Lung 6</td>
<td>III</td>
<td>BIBW 2992 40 mg/daily 2:1 versus cisplatin+gemcitabine</td>
<td>I</td>
<td>Adenocarcinaoma No prior CT or EGFR TKI ECOG 0-1 EGFRm+</td>
</tr>
<tr>
<td>BI 1200.40</td>
<td>II</td>
<td>BIBW 2992 50 mg/daily</td>
<td>I</td>
<td>Adenocarcinaoma or BAC ECOG 0-2 EGFR FISH+</td>
</tr>
<tr>
<td>BI 1200.41</td>
<td>II</td>
<td>BIBW 2992 50 mg/daily</td>
<td>I</td>
<td>up to III depending on the cohort Adenocarcinaoma Cohort 1 (EGFR+): SD after 1 line EGFR TKI Cohort 2 (EGFR- and EGFR FISH+): up to 3 lines of CT, no prior EGFR TKI Cohort 3 (HER2+): no restriction</td>
</tr>
<tr>
<td>BI 1200.70</td>
<td>Ib</td>
<td>BIBW 2992 50 mg/daily +sirolimus</td>
<td>II-III</td>
<td>Adenocarcinaoma PD after 1 lines CT PD after 1 line EGFR TKI in EGFR+/−m ECOG 0-2</td>
</tr>
</tbody>
</table>


Simultaneous EGFR/HER2 inhibition may interrupt the possibility of heterodimerization leading to improve the efficacy and BIBW 2992 is currently the most advanced compound in this class (95). BIBW 2992 is an irreversible inhibitor of EGFR/HER1 and HER 2 under investigation in several trials in first and second line for NSCLC patients with or without a selection driven by EGFR mutational status.

In the phase II LUX-Lung 2 trial, patients with adenocarcinoma and harbouring EGFR activating mutations were treated with BIBW 2992 50 mg/day in first line and second line treatment. Among 129 patients (61 as first and 68 as second line therapy) the confirmed RR in the overall population is 60% (64% in those patients with deletion 19/L858R) median PFS 14 months and OS 24 months. Similar to the other EGFR TKIs, diarrhoea and skin adverse events are the most common toxicities, that appeared to be reduced at 40 mg/day (96). A phase II/III trial of BIBW 2992 plus best supportive care (BSC) versus placebo plus BSC (LUX-Lung 1) is ongoing in patients who progressed after one or two lines of chemotherapy as well as a phase III (LUX-Lung 3) is still open with BIBW 2992 as a first line therapy versus pemetrexed/cisplatin in mutated NSCLC patients (unpublished data). A summary of drug development in lung cancer is shown in Table I.

PF00299804 is an oral irreversible inhibitor of EGFR/HER1, HER2 and HER 4, which demonstrated efficacy in a phase II trial evaluating NSCLC patients after failure of prior chemotherapy and erlotinib. In a preliminary analysis of 36 evaluable patients with T790M mutation grade 3 toxicities included skin toxicity, diarrhoea, fatigue and vomiting (97).

The same molecule has been tested as a first line therapy in advanced adenocarcinoma never or light smokers or with activating EGFR mutations. The
EGFR pathway in advanced NSCLC

preliminary data on 39 patients enrolled, suggest encouraging activity of PF0029980445 mg/day and tumours shrinkage was seen in all evaluable patients with EGFR mutant disease (N=14): preliminary PFS rates at 3,4 and 6 months were 90%, 79% and 79%, respectively (98).

HKI-272 is an EGFR, HER2/neu (erbB2) and HER3 inhibitor that has been evaluated in phase I trial in solid tumours showing IHC expression of either EGFR or HER2 (99, 100). No responses were seen in this trial, but a stabilization of the disease in 5 patients, who previously received EGFR TKIs, was shown. A 3 arm phase II trial was then conducted: the enrolment is complete, but data are not yet available (101).

Several TKI targeting both EGFR and VEGF pathway are in development and most advanced of these compounds is vandetanib. The four phase III trials evaluating vandetanib in second line setting therapy for NSCLC have already been presented: two considered the experimental drug with chemotherapy(docetaxel or pemetrexed), while the other two were designed with vandetanib as monotherapy versus erlotinib or placebo (102, 103, 104).

The ZEAL trial did not reach its primary end point, while in the ZODIAC trial vandetanib plus docetaxel significantly improved PFS (HR: 0.79, p<0.001) but not OS when compared to docetaxel alone (103, 104).

The ZEST and the ZEPHIR trials did not met their primary end points of PFS and OS, respectively (102, 105).

Downstream mediators of EGFR provide many new opportunities for therapeutic intervention in NSCLC and many TKIs, small molecule and monoclonal antibodies are currently under evaluation.

AZD6244 is a MEK1/2 inhibitor under evaluation in a phase II trial in NSCLC patients with specific mutations such as B-raf, which has been shown in preclinical models to sensitize tumour cells to MEK inhibition (106). The same molecule is currently investigated in phase II trial versus pemetrexed in NSCLC patients who progressed after one or two lines of chemotherapy.

Among monoclonal antibodies, panitumumab and matuzumab are being evaluated in NSCLC.ARO 197 is a novel, selective, non-ATP competitive tyrosine kinase inhibitor with a broad-spectrum anti tumour activity in a number of xenografts model including NSCLC. The role of c-MET pathway is well established in lung cancer: c-MET amplification is associated with resistance to EGFR kinase inhibitors in NSCLC cells and in vivo antitumor activity of ARQ added to EGFR TKI is greater than either drug alone (107). At 2010 ASCO annual meeting a randomized phase II trial comparing erlotinib plus ARQ 197 to erlotinib plus placebo in previously treated EGFR-inhibitor naive patients with advanced NSCLC was presented showing an advantage from the addiction of ARQ 197 to erlotinib in terms of PFS (16.1 versus 9.7 weeks). The benefit in terms of PFS and OS was particularly evident in non-squamous population and in a molecularly-selected subgroup of cases including EGFR WT and K-ras mutation positive patients (108).

7. REFERENCES


EGFR pathway in advanced NSCLC


EGFR pathway in advanced NSCLC


33. V. A. Miller, P. O’Connor, C. Soh and F Kabbinavar: A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemoradiotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC) J Clin Oncol 27 (June 20 suppl), abs LBA8002 (2009)

34. F. F. Kabbinavar, V. A. Miller, B. E. Johnson, P. G. O’Connor, C. Soh, ATLAS Investigators: Overall survival (OS) in ATLAS, a phase IIIb trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC) J Clin Oncol 28 (May 20 suppl), abs 7526 (2010)


40. M. Fukuoka, Y. P. Wu, S. Thongprasert, D. Yang, N. Chu and C. Saito: Biomarker analyses from a phase III, randomized, open-label, first-line study of gefitinib (G) versus carboplatin/paclitaxel (C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) in Asia (IPASS) J Clin Oncol 27 (May 20 suppl.), abs 8006 (2009)


512
EGFR pathway in advanced NSCLC


52. RS Herbst, AM Maddox, ML Rothenberg, EJ Small, EH Rubin, J Baselga, F Rojo, WK Hong, SD Averbuch, J Ochs, PM LoRusso: Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non–small-cell lung cancer and other solid tumors: Results of a phase I trial. J Clin Oncol 20, 3815-3825 (2002)


58. R Maruyama, Y Nishiwak, T Tamura, N Yamamoto, M Tsuboi, K Nakagawa, T Shinkai, S Negro, F Imamura, K Eguchi, K Takeda, A Inoue, K Tomii, M Herada, N Masuda, Y Itoh, N Saijo, M Fukuoku: Phase III study, V-
EGFR pathway in advanced NSCLC


EGFR pathway in advanced NSCLC


EGFR pathway in advanced NSCLC

Key Words: EGFR, non-small cell lung cancer, Gefitinib, Erlotinib, Cetuximab, Maintenance Therapy, Review

Send correspondence to: Silvia Novello, Thoracic Oncology Unit, University of Turin, AUO San Luigi, Regione Gonzole 10; 10043 Orbassano (TO) Italy, Tel: 00390119026978, Fax 00390119038616, E-mail silvia.novello@unito.it

http://www.bioscience.org/current/vol3S.htm