Published in final edited form as:

Drugs. 2012 June 19; 72(0 1): . doi:10.2165/1163018-S0-000000000-00000.

Role of Erlotinib in the Treatment of Non-Small Cell Lung Cancer:

Clinical Outcomes in Wild-Type Epidermal Growth Factor Receptor Patients

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Abstract

Erlotinib is an orally administered small molecule inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase. Erlotinib at the standard oral daily dose of 150mg is approved for the treatment of unselected chemorefractory advanced non-small cell lung cancer patients as well as maintenance therapy after first-line chemotherapy. The European Medicines Agency has recently also approved erlotinib as the first-line therapy in patients with *EGFR* mutations. Although recent studies have identified higher response rates and improved survival with erlotinib in a subset of patients with *EGFR* mutations, the survival benefit from single agent erlotinib in chemorefractory patients and in the maintenance setting is well observed in *EGFR* wild-type patients. The role of single agent erlotinib in the first-line setting in special subsets of *EGFR* wild-type patients (elderly, poor performance status, nonsmokers) needs to be further determined. The combination of erlotinib with other targeted therapies has shown promising results and warrants further studies in *EGFR* wild-type patients.

1. Introduction

Lung cancer is the leading cause of cancer-related death in the USA and all over the world.^[1] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers. The majority of patients with NSCLC are diagnosed at an advanced stage.^[2] Chemotherapy offers symptomatic relief and modest improvement in survival. The responses are, however, brief and the effectiveness of chemotherapy has reached a plateau in improving the outcome in NSCLC patients.^[3]

The epidermal growth factor receptor (EGFR) family of genes encodes widely expressed transmembrane protein tyrosine kinases that have been implicated in the development and progression of human cancer.^[4] NSCLC frequently expressed EGFR and targeting the EGFR pathway is of great interest in the treatment of NSCLC. Erlotinib is an orally administered small molecule inhibitor of EGFR tyrosine kinase. Erlotinib is approved as a single agent in refractory NSCLC as well as maintenance therapy after platinum-based doublets.^[5] In this review, we will discuss the clinical outcome of erlotinib in NSCLC patients with *EGFR* wild type.

2. Epidermal Growth Factor Receptor Pathway in Lung Cancer

EGFR is a transmembrane protein implicated in the development and progression of cancers. EGFR belongs to a family of four transmembrane cell surface receptors called the

ErB family.^[6] EGFR binds with high affinity to several ligands including EGF, amphiregulin and transforming growth factor alpha. Upon ligand binding, the receptors form homodimers or heterodimers and autophosphorylate tyrosine residues in the cytoplasmic domain triggering a cascade that leads to cellular proliferation, angiogenesis, metastasis and inhibition of apoptosis.^[7]

EGFR is expressed in the majority of NSCLC. Targeting EGFR has become a viable treatment option for patients with advanced NSCLC. Two major classes of inhibitors of EGFR have been developed: anti-EGFR monoclonal antibodies (cetuximab and panitumumab) and small-molecule EGFR tyrosine kinase inhibitors (gefitinib and erlotinib). Erlotinib is an orally administered small molecular inhibitor of EGFR tyrosine kinase.^[8,9] In lung cancer cell lines, erlotinib causes G0/G1 cell cycle arrest and inhibits cancer cell proliferation.^[10] In sensitive cells, erlotinib causes tumour cell apoptosis.^[11] Inhibition of the EGFR pathway has also been shown to have an anti-angiogenic effect through the inhibition of angiogenic growth factor production.

A subgroup of patients with NSCLC harbours mutations in the tyrosine kinase domain of the *EGFR* gene.^[12,13] The incidence of *EGFR* mutations is particularly common in adenocarcinoma and in patients who are women and non-smokers.^[14] The incidence of mutation ranges from 20% to 40% in the east and southeast Asian patient population to 5–19% in western countries.^[15,16] In a large-scale study performed in Spain, lung cancers from 2105 patients were screened for *EGFR* mutations. *EGFR* mutations were found in 350 of 2105 patients (16.6%). The presence of *EGFR* mutation is associated with good prognosis and predicts responsiveness to erlotinib and gefitinib.^[17,18] The role of erlotinib in *EGFR* mutated patients will be the subject of a separate review.

The majority of patients with NSCLC, however, did not harbour *EGFR* mutations and are considered *EGFR* wild type. Here we will review the clinical outcome of erlotinib in patients with NSCLC, who have *EGFR* wild type.

3. Erlotinib: Single Agent Activity in Epidermal Growth Factor Receptor Wild-Type Patients

The initial studies of erlotinib in NSCLC patients were performed in patients with NSCLC, in whom the *EGFR* mutation status was either unknown or not tested. A number of large randomized trials evaluating erlotinib have performed *EGFR* mutation testing in available tissues. The tissue ascertainment rate in those trials varies. The majority of the trials were performed in western countries where the incidence of the *EGFR* mutation is 5–19%. Although the response rate with erlotinib is significantly higher in patients with *EGFR* mutations, the survival benefit with erlotinib, albeit small, is maintained in patients with *EGFR* wild type. Here we will review the clinical data from trials involving erlotinib as a single agent in unselected patients as well as *EGFR* wild-type NSCLC patients.

3.1 Single Agent Erlotinib in Chemorefractory Patients

The pivotal phase III trial (BR.21) evaluated single agent erlotinib in previously treated patients with NSCLC. A total of 731 patients who had received one or two previous chemotherapy regimens was randomly assigned in a 2:1 ratio to receive oral erlotinib 150mg a day or placebo. The majority of these patients had metastatic disease, 49% had received two previous chemotherapy regimens and 93% had received platinum-based chemotherapy. The majority of patients (50%) in the trial had a histological subtype of adenocarcinoma and 30% of patients had squamous cell histology. The response rate was 8.9% in the erlotinib group compared with less than 1% in the placebo group ($p < 0.001$). The median duration of response was 7.9 months in the erlotinib arm compared with 3.7 month in the placebo group.

The progression-free survival (PFS) and overall survival (OS) were 2.2 months and 6.7 months in the erlotinib-treated group compared with 1.8 months and 4.7 months in the placebo arm. Rash and diarrhoea were the main side effects with erlotinib, resulting in dose reduction in 12% and 5% of erlotinib-treated patients, respectively. On the basis of these results, erlotinib is approved for the treatment of chemorefractory NSCLC patients.^[19]

Quality of life (QoL) assessments were also performed in the BR.21 study with the compliance rate of 87% at baseline and over 70% during the treatment. The primary endpoint was time to deterioration of three common lung cancer symptoms: cough, dyspnoea and pain. Patients treated with erlotinib had significantly longer median time to progression of all three symptoms: 4.9 versus 3.7 months for cough ($p = 0.04$); 4.7 versus 2.9 months for dyspnoea ($p = 0.04$); and 2.9 versus 1.9 months for pain ($p = 0.01$). Approximately 45% of patients receiving erlotinib showed an improvement in these symptoms during treatment, and this was associated with a significant improvement in physical function and global QoL.^[20]

The tumour biopsy specimens from participants in the BR.21 trial were evaluated for EGFR expression by immunohistochemistry (325/731 patients), *EGFR* mutations by reverse transcription–polymerase chain reaction (197/731 patients) and *EGFR* gene copy numbers by fluorescence in-situ hybridization (221/731 patients). The *EGFR* mutation was detected in 40 (23%) of 197 patients tested, with 13 patients having exon 19 deletion and eight patients with exon 21 L858R. The response rate with erlotinib in patients with *EGFR* mutations was more than twice that among patients with *EGFR* wild type, although this was not statistically significant. However, mutational status had no significant effect on survival. The risk of death did not differ significantly among patients with *EGFR* mutations or among patients with *EGFR* wild type. In multivariate analyses, adenocarcinoma ($p = 0.01$), never smoker ($p < 0.001$) and the expression of EGFR ($p = 0.03$) were associated with an objective response. The survival after treatment with erlotinib was, however, maintained in all statuses including *EGFR* wild-type patients and was not influenced by the status of EGFR expression, the number of EGFR copies or *EGFR* mutations.^[21]

The safety and efficacy of single agent erlotinib was also examined in a large global phase IV post-marketing study. In the global phase IV Tarceva Lung Cancer Survival Treatment study, 6580 patients who had previously been treated with chemotherapy, radiotherapy or were unsuitable for those treatments were treated with erlotinib 150 mg a day. The disease control rate was 69% in 5394 patients for whom the best response data were available. The median PFS and OS were 3.25 and 7.9 months, with a 1-year survival rate of 37.7% in this heterogeneous unselected group of patients. Only 4% of patients experienced erlotinib-related serious adverse events. Dose reduction was reported in 17% of patients and the majority of this was associated with erlotinib-related adverse events, mainly rash and diarrhoea.^[22]

A separate phase IIIb multicentre, open-label trial evaluated erlotinib 150mg a day in 229 patients with previously treated advanced NSCLC. The overall response rate was 8.3% [95% confidence interval (CI) 5.2%, 2.4%] with an OS of 6.3months (95% CI 4.7, 8 months). The response rate in never-smokers, previous smokers and current smokers was 28.6%, 6% and 7.3%, respectively. The median OS was not reached in non-smokers and was 5.2 and 6.3 months in previous and current smokers.^[23]

The Okayama Lung Cancer Study Group examined single agent erlotinib 150 mg a day as monotherapy in previously treated Japanese patients with *EGFR* wild type. Thirty patients were enrolled in the trial with an objective response rate of 3.3%. The median PFS and OS were 2.1 and 9.2 months, consistent with other studies in refractory disease.^[24]

In another large randomized study, the efficacy and tolerability of second-line erlotinib was compared with standard second-line chemotherapy with either pemetrexed or docetaxel in patients with advanced NSCLC. Approximately 425 patients were enrolled in the study and the primary endpoint was OS. The second-line erlotinib was associated with a similar median OS duration to pemetrexed or docetaxel in patients with advanced NSCLC [5.3 versus 5.5 months; hazard ratio (HR) 0.96 in the overall population; 95% CI 0.78, 1.19]. In the subgroup analysis of 149 patients with *EGFR* wild type, there was no difference in OS between the treatment groups (HR 0.85; 95% CI 0.59, 1.22) (figure 1). In terms of safety there were fewer treatment-related deaths and withdrawals as a result of adverse events in the erlotinib group, and the most common event was mild-to-moderate skin rash.^[25]

3.2 Single Agent Erlotinib as Maintenance Therapy

Single agent erlotinib has also been evaluated as maintenance therapy in patients with advanced NSCLC after a defined number of initial chemotherapy cycles.^[26] The Sequential Tarceva in Unresectable Lung Cancer (SATURN) trial is a phase III trial evaluating erlotinib compared with placebo in patients with advanced NSCLC who had non-progressive disease following four cycles of first-line platinum-based doublet chemotherapy. A total of 889 patients who did not have progressive disease after an initial four cycles of chemotherapy was randomly assigned in a 1:1 ratio to either oral erlotinib 150 mg a day or placebo. The co-primary endpoints of the study were PFS in all patients and PFS in patients who had *EGFR* overexpression by immunohistochemistry. The median PFS in the erlotinib group was 12.3 weeks compared with 11.1 week in the placebo group (HR 0.71, 95% CI 0.62, 0.82, $p < 0.0001$). The proportion of patients with PFS at 6 months was 25% (95% CI 21%, 29%) in the erlotinib arm compared with 15% (95% CI 12%, 19%) in the placebo arm. The overall response rate was 11.9% in the erlotinib arm compared with 5.4% in the placebo arm ($p = 0.0006$).^[27]

EGFR mutation analysis data were available in 60% of the patients in the trial. The majority of the patients in the trial had *EGFR* wild type. The activating mutations in *EGFR* were detected in 49 patients: 22 patients in the erlotinib arm and 27 patients in the placebo arm. The benefit of erlotinib maintenance on PFS was very prominent in *EGFR* mutated patients (HR 0.10, 0.04–0.25, $p < 0.001$). However, *EGFR* wild-type patients also benefited from erlotinib maintenance (HR 0.78, 0.63–0.96, $p = 0.0185$). The benefit of erlotinib was maintained regardless of performance status (PS), age, smoking status, ethnic origin or histology (squamous or adenocarcinoma).^[28]

In the intent-to-treat population, the median OS was 12 months in the erlotinib arm compared with 11 months in placebo (HR 0.81, 95% CI 0.70, 0.95, $p = 0.0088$). This OS benefit was maintained in patients with *EGFR* wild type (HR 0.77, 0.61–0.97). The safety and tolerability data of erlotinib in maintenance therapy was very similar that seen in the phase III BR.21 study, with rash and diarrhoea as the most common adverse events. The serious adverse events were reported in 47 patients (11%) in the erlotinib arm compared with 34 patients (8%) in the placebo arm. Seventy patients (16%) in the erlotinib arm required a dose reduction or interruption because of an adverse event compared with 15 patients (3%) receiving placebo.^[27,28]

The SATURN trial also included a QoL assessment using the FACT-L QoL instrument. There was no statistically significant difference in QoL for patients receiving erlotinib compared with placebo. A post-hoc analysis showed that time to pain and analgesic use were both significantly improved but time to cough and dyspnoea were not significantly affected.^[27]

3.3 Single Agent Erlotinib as First-Line Therapy

Several phase II trials have evaluated single agent erlotinib as the first-line therapy in either selected or unselected patients with metastatic NSCLC. In the Eastern Cooperative Oncology Group (ECOG) 3503 trial, 137 unselected patients with advanced NSCLC with no previous history of targeted therapy or chemotherapy for metastatic disease were treated with single agent oral erlotinib 150 mg a day. The objective response rate was 6.9%, and 31% of patients had stable disease. Forty-three patients had tumour samples that were analysable for *EGFR* mutations and three patients had an activating mutation in *EGFR*. There was no difference in the objective response rate between mutant and *EGFR* wild type. The median OS of all patients was 7.9 months (95% CI 5.5, 11.7 months). The *EGFR* mutated patients had OS of 33 months compared with 6 months for *EGFR* wild type.^[29]

In another phase II study, 80 patients with chemotherapy-naïve advanced NSCLC aged over 70 years were treated with erlotinib 150mg a day until disease progression or significant toxicity. The objective response rate was 10%, and 41% of patients had stable disease. The median time to progression was 3.5 months (95% CI 2, 5.5 months) and OS was 10.9 months (95% CI 7.8, 14.6 months). The 1 and 2-year survival rates were 46% and 19%, respectively. The *EGFR* mutation was studied in 43 patients and nine patients had activating mutations. The median OS in 34 patients with *EGFR* wild type was 8.1 months with 38% 1-year survival compared with the median survival of more than 15 months with 89% 1-year survival in nine patients with *EGFR* mutations.^[30]

In a multi-institutional phase II study, 101 patients with bronchoalveolar carcinoma (BAC) (n = 12) and adenocarcinoma BAC subtype (n = 89) were treated with erlotinib 150mg a day. The overall response rate was 22% (95% CI, 14%, 31%): 20% in patients with pure BAC versus 23% in patients with adenocarcinoma, BAC subtype. The OS was 4 months and 19 months in pure BAC and those with adenocarcinoma, BAC subtype, respectively. *EGFR* mutation testing was performed in 81 patients. The response rate in 63 patients with *EGFR* wild type was 7% with the corresponding PFS and OS of 2 and 17 months, respectively. In contrast, 18 patients with *EGFR* mutations had a response rate of 83% with the corresponding PFS and OS of 13 and 23 months, respectively. The authors concluded that erlotinib is active in BAC and adenocarcinoma, mixed subtype BAC.^[31]

In a randomized phase II study, erlotinib 150 mg a day was compared with erlotinib 150 mg a day with carboplatin (area under the curve 6) and paclitaxel 200mg/m² as the first-line therapy in never/light former smokers with advanced NSCLC. Overall, 182 patients were randomly assigned: 82 patients to erlotinib alone and 100 patients to erlotinib and chemotherapy. Over 80% of patients in the study were Caucasians and approximately 60% were women. The overall response rate was 34% with erlotinib monotherapy compared with 47% with erlotinib and chemotherapy. The PFS and OS were 6.7 and 24 months in the erlotinib arm compared with 6.0 and 19.6 months in the erlotinib and chemotherapy arm. *EGFR* mutation analysis was performed in 172 patients (95%), and 32 patients in the erlotinib alone arm and 35 patients in the erlotinib and chemotherapy arm had *EGFR* mutations. The response rate with erlotinib alone in *EGFR* wild-type patients (n = 48) was 8% with a median PFS of 2.8 months and OS of 15.4 months, very similar to the rates in second and third-line studies. The overall response rate was 31% in *EGFR* wild-type patients treated with erlotinib and chemotherapy. The median PFS and OS were 4.8 months and 13.7 months in this group; not statistically significant from the erlotinib alone arm. The authors concluded that erlotinib alone had the same efficacy with less toxicity than erlotinib plus chemotherapy in this selected population of predominantly Caucasian never/light smokers with advanced NSCLC.^[32]

Single agent erlotinib has also been extensively studied in patients with advanced NSCLC who had poor PS (ECOG PS 2) or are unsuitable for chemotherapy. In the multicentre phase II trial conducted by the Southwest Oncology Group, 81 patients with advanced NSCLC and a PS of 2 were treated with erlotinib 150 mg a day. The overall response rate was 8% (95% CI 3%, 16%) with a disease control rate (complete response/partial response/stable disease) of 42%. PFS and median survival were 2.1 months (95% CI 1.5, 3.1) and 5 months (95% CI 3.6, 7.2), respectively, with a corresponding 1-year survival of 24% (95% CI 15%, 34%). The treatment was generally well tolerated. However, grade 3 to 4 toxicity was reported in 30 patients (40%), including fatigue (16%), rash (9%), diarrhoea (7%) and anorexia (7%). There was one possible treatment-related death (pneumonitis).^[33]

In a large randomized phase III trial conducted in the UK, single agent erlotinib 150 mg a day plus best supportive care was compared with placebo plus best supportive care in chemonaive, poor PS advanced NSCLC patients (ECOG PS 2/3 or PS 0/1 unfit for platinum chemotherapy; stage IIIB/IV). Overall, 670 patients were randomly assigned to either erlotinib (350) or placebo (320), from 78 UK centres. The primary endpoints were OS, PFS, response rate and toxicity. The median age was 77 years (range 42–91), 38% of patients had adenocarcinoma and 39% of patients had squamous cell histology. The percentage of patients with ECOG PS score of 0/1, 2 and 3 was 16%, 55% and 29%, respectively. The study did not meet the primary endpoint. Overall, erlotinib plus best supportive care did not improve OS; the HR (erlotinib versus placebo for OS) was 0.98; 95% CI 0.82, 1.15, $p = 0.77$. However, there was some evidence of benefit for PFS (HR 0.86, 0.74–1.01, $p = 0.07$).^[34]

In a prespecified subgroup analysis, significantly longer OS and PFS were observed favouring the erlotinib arm in female patients (HR 0.75, 0.57–0.99, $p = 0.04$ and HR 0.64, 0.49–0.83, $p = 0.001$, respectively). The median survival was 5.3 months in the erlotinib group compared with 4.3 month in the placebo group, with the corresponding 1-year survival rate of 24% versus 18% favouring erlotinib in female patients. The survival benefit with erlotinib seen in female patients was maintained in both adenocarcinoma and non-adenocarcinoma patients. *EGFR* mutations were tested in 311 patients and 3.5% (11/311 patients) had *EGFR* mutations. In patients with *EGFR* wild type, there was no survival benefit with erlotinib in male patients (HR 1.03, 95% CI 0.77, 1.39, $p = 0.82$). The survival benefit with erlotinib was, however, maintained in *EGFR* wild-type female patients (HR 0.58, 95% CI 0.39, 0.87, $p = 0.009$). As expected, increased grade 3/4 rashes and diarrhoea were observed in patients receiving erlotinib.^[34]

In a multicentre randomized phase II trial single agent erlotinib 150mg a day was compared with standard chemotherapy with four cycles of carboplatin (area under the curve 6) and paclitaxel (200 mg/m² on day 1 every 3 weeks) as firstline therapy in advanced NSCLC patients with a PS of 2. Patients who experienced progression or did not tolerate or refused further chemotherapy were allowed to cross over to erlotinib. The primary endpoint was PFS. Fifty-two patients were randomly assigned to erlotinib and 51 to chemotherapy. Partial responses were 2% and 12%, respectively. The median PFS was 1.9 months in the erlotinib arm and 3.5 months in the chemotherapy arm (HR 1.45, 95% CI, 0.98, 2.15, $p = 0.06$). Median survival times were 6.5 and 9.7 months, respectively (HR 1.73, 95% CI, 1.09, 2.73, $p = 0.018$). Patients who crossed over to erlotinib had a median survival of 14.9 months. Rash and diarrhoea were more common with erlotinib; emesis, alopecia, peripheral neuropathy and fatigue were more common with chemotherapy. The QoL was similar between the two arms. The authors concluded that unselected patients with advanced NSCLC and a PS of 2 are best treated with combination chemotherapy as first-line therapy. Erlotinib may be considered in patients selected by clinical or molecular markers.^[35]

In summary, the role of single agent erlotinib as first-line therapy in patients with *EGFR* wildtype NSCLC is not very well defined. On the basis of the randomized trial, single agent erlotinib may improve survival in a subset of female patients who have poor PS and are not suitable for chemotherapy. However, the final data from that study have yet to be reported.

4. Erlotinib in Combination with Other Targeted Therapies

Erlotinib has also been evaluated with several other targeted therapies including inhibitors of the vascular endothelial growth factor receptor pathway, c-met pathway and others. Of particular interest is the combination of erlotinib with c-met inhibitors in *EGFR* wild-type patients.

The hepatocyte growth factor and its receptor c-met pathway (c-met) also cross-interact with the *EGFR* pathway. Dual *EGFR* and c-met inhibition has been proposed as a promising strategy for overcoming met-mediated resistance to *EGFR* inhibitors.^[36] The combination of erlotinib and c-met inhibitors has been explored in randomized phase II studies. ARQ197 is an orally administered selective, non-adenosine triphosphate competitive inhibitor of c-met.^[37] In a randomized placebo controlled, double-blind phase II trial, 167 patients with advanced NSCLC were treated with erlotinib plus ARQ197 or erlotinib plus placebo. The primary endpoint was PFS. The median PFS was 16.1 weeks in erlotinib plus ARQ197 compared with 9.7 weeks in the erlotinib plus placebo arm (HR 0.81, 95% CI 0.57, 1.15, $p=0.23$). A planned multivariable Cox regression model adjusting for prognostic factors including histology and genotype showed that the improvement in the PFS in the combination arm was maintained (HR 0.68, 95% CI 0.47, 0.98, $p < 0.05$). The PFS improvement was particularly prominent among patients with non-squamous histology, *EGFR* wild-type status and *K-RAS* mutations. The safety analysis revealed no major differences between arms with expected adverse events (10% of patients; all grades) including rash (64/52%), diarrhoea (48/53%), fatigue (33/37%), nausea (26/26%) and anaemia (14/13%). The combination of erlotinib and ARQ-197 was well tolerated and prolonged PFS in the treatment of second/thirdline *EGFR* inhibitor-naïve NSCLC. Of particular interest is the benefit observed among patients with non-squamous histology, *k-RAS* mutations and *EGFR* wild-type status. An ongoing phase III study will be evaluating the combination of erlotinib and ARQ 197 in advanced NSCLC patients.^[38]

5. Erlotinib in Smokers

The influence of smoking status on the clinical outcome in patients with advanced NSCLC has also been an area of great interest. In initial trials, the improvement in survival with erlotinib is much more pronounced in non-smokers. As mentioned previously, the *EGFR* mutations are more frequent in female patients with adenocarcinoma who are non-smokers. In the BR.21 trial, however, the survival benefit with erlotinib was maintained in male smokers with squamous histology. In addition, cigarette smoking induces CYP1A1/1A2 and alters the pharmacokinetics of erlotinib.

In a phase I dose escalation study, a cohort of 22 patients with advanced NSCLC who had been smoking 10 or more cigarettes per day for 1 year or more received escalating doses of erlotinib for 14 days until dose-limiting toxicity. The doselimiting toxicity was observed in two out of five patients at a daily dose of erlotinib of 350 mg. The maximum tolerated dose of erlotinib in smokers was 300 mg a day. A separate cohort of 35 patients was randomly assigned to either erlotinib 150 mg a day or erlotinib at the maximum tolerated dose (300 mg/day) with a pharmacokinetic assessment at day 14. The steady state trough plasma concentration and the incidence of rash and diarrhoea with 300 mg erlotinib a day in smokers were similar to those in former or never smokers receiving 150 mg erlotinib a day

in earlier studies. Further studies are needed with higher dose of erlotinib in current smokers.^[39]

6. Conclusion

Erlotinib has been extensively studied in clinical trials in patients with advanced NSCLC. Although the response rate with erlotinib is higher in a subset of patients with the *EGFR* mutation, the survival benefit from single agent erlotinib in chemorefractory patients and in the maintenance setting is well observed in *EGFR* wild-type patients. The role of single agent erlotinib in the first-line setting in special subsets of *EGFR* wildtype patients (elderly, poor PS, non-smokers) needs to be further determined. The combination of erlotinib with other targeted therapies has shown promising results and warrants further studies in *EGFR* wild-type patients.

Acknowledgments

Prof. Perez-Soler has received honoraria for consultancies from Roche and Genentech USA Inc; Dr Piperdi has received honoraria from Genentech USA Inc, Bayer and Onyx Pharmaceutical.

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Fig. 1.
Kaplan–Meier curve for overall survival in patients with *EGFR* wild-type tumour. **EGFR**=
epidermal growth factor receptor; **HR**= hazard ratio.