Clinical Medicine Insights: Oncology

REVIEW

The Evolving Role of Maintenance Therapy Using Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs) in the Management of Advanced Non-Small-Cell Lung Cancer

Chao H. Huang[1,2] and Benjamin C. Powers[3]

[1]Associate Professor, University of Kansas Medical Center, Kansas City, KS. [2]Veteran's Administration Medical Center, Kansas City, MO. [3]Hematology and Medical Oncology Fellow, University of Kansas Medical Center, Kansas City, KS. Corresponding authour email: chuang2@kumc.edu; bpowers@kumc.edu

"Time is the measurer of all things, but is itself immeasurable, and the grand discloser of all things, but is itself undisclosed."
CHARLES CALEB COLTON, *Lacon*

Abstract: The epidermal growth factor receptor (EGFR) plays an important role in the development of many cancers, including non-small cell lung cancer. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) are a class of novel biologically-targeted agents widely used in the management of recurrent non-small cell lung cancer. Erlotinib, one of the EGFR TKIs, is currently FDA approved in second and third line therapy. However, recent studies showed that erlotinib is also effective as maintenance therapy after initial chemotherapy, improving disease free survival and possibly overall survival. Our current understanding of erlotinib's mechanism of action, with the discovery that EGFR mutation confers higher response rate, has propelled this agent into the first line setting. Advances in molecular testing and clinical research of this agent and other agents in this class will eventually change the way we utilize EGFR TKIs in the near future.

Keywords: EGFR TKI, lung cancer maintenance

Video Abstract Available from http://la-press.com/t.php?i=va5127

Clinical Medicine Insights: Oncology 2012:6 137–147

doi: 10.4137/CMO.S5127

This article is available from http://www.la-press.com.

Introduction

Life is unexpectedly abbreviated for patients newly diagnosed with advanced lung cancer. Despite an impressive national anti-tobacco campaign and exciting new targeted therapies, lung cancer remains the leading cause of cancer mortality among men and women in the United States, with non-small-cell lung cancer (NSCLC) accounting for the vast majority of lung cancer cases. In 2012, the American Cancer Society estimates 226,160 new cases of lung cancer in the United States. The prognosis of this disease is dismal, with an astonishing 70% (160,340 patients) of those newly diagnosed dying within the first year.[1] This means 439 deaths a day, and in the twenty minutes it takes the reader to finish reviewing this manuscript, another 5 patients will have died of lung cancer. Even though the number of deaths in lung cancer exceeds the number of deaths of breast, colon and prostate cancer combined, the funding for lung cancer research is far behind the amount poured into these other cancers. The National Lung Cancer Partnership estimates that $37,616 research dollar per death is directed towards breast, colorectal and prostate cancer research combined. In contrast, lung cancer receives $1,675 research dollar per death.[2]

Most patients with NSCLC are diagnosed at an advanced stage of disease, and therefore, treatment goal is usually palliative in nature. In patients with advanced stage NSCLC and with good performance status (Eastern Cooperative Oncology Group performance status 0 or 1), the standard of care involves four to six cycles of a platinum-based double-agent regimen which has shown to extend overall survival (OS) to a median of 10 to 13 months, reduce disease-related symptoms, and improve quality of life.[3–6] Three of five patients with advanced stage NSCLC will have disease control at eight weeks with platinum-based regimens.[7] Despite numerous randomized trials comparing different combination chemotherapy regimens, no doublet regimen has proven to be superior. Several clinical studies investigated the role of extending platinum-based chemotherapy beyond the four cycles in those with stable disease, but they revealed similar survival and more toxicity in the extended duration of platinum-based therapy.[8–12] Current standard of care is a finite number of chemotherapy treatments, despite the fact that the disease will invariably progress in the future. Due to this bleak outcome, a strategy other than extending platinum-based chemotherapy is desirable, in hopes of continued overall survival benefit and a reduction in disease-related symptoms, while maintaining a satisfactory quality of life.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) were first studied in recurrent lung cancer patients in the 1990s. The first compound studied, gefitinib, showed therapeutic activity in phase II trials with patients with recurrent advanced non-small cell lung cancer.[13] Although gefitinib has subsequently been withdrawn from the United States market due to lack of efficacy in the phase III ISEL trial,[14] there were anecdotal reports of dramatic response with gefitinib. Clearly not all patients benefited from this agent, but patients with certain clinical characteristics were identified as predictive of response; these included female gender, adenocarcinoma histology, Asian ancestry and non-smokers.[15] This was also observed in the BR 21 trial[16] using erlotinib, which eventually led to approval of this agent in recurrent lung cancer in 2004. The exact mechanism of action of the EGFR TKIs was later elucidated by Lynch and Paez, describing a specific mutation in the EGFR tyrosine binding site.[17,18] (Fig. 1) EGFR is critical in many cell-signaling pathways that influence nuclear gene activation, cell division, apoptosis, motility and adhesion; when EGFR is overexpressed, as is the case in many tumor types,[19] tumorigenesis and tumor growth are accelerated. Competing with adenosine triphosphate, erlotinib hydrochloride, reversibly binds to the intracellular catalytic domain of epidermal growth factor receptor (EGFR) tyrosine kinase, thereby inhibiting phosphorylation and blocking the signal transduction events and tumorigenic effects associated with EGFR activation.

Erlotinib is orally administered and is about 60% absorbed, but its bioavailability is substantially increased by food to almost 100%, as the solubility is pH dependent. Peak plasma levels occur four hours after dosing, and the plasma level is reduced by cigarette smoking.[20] Therefore, erlotinib would be theoretically less effective in smokers due to lower serum levels. Erlotinib is metabolized predominantly by CYP3A4; therefore, inhibitors of CYP3A4 would

be expected to increase drug exposure and conversely CYP3A4 inducers would be expected to decrease efficacy. Approximately 80% of the drug is excreted in the feces, and its use should be used with extra caution in patients with a total bilirubin greater than three times the upper limit of normal.[21]

The side effect profile of the EGFR TKIs is much more tolerable than traditional chemotherapy agents. In the past, conventional cytotoxic chemotherapy was given for a limited number of cycles mainly due to increased toxicities and limited therapeutic advantage.[22] This is not the case with EGFR TKIs. In fact, grade 3 and 4 toxicities most often attributed to these drugs are rash and diarrhea, rarely the cause of discontinuation of therapy. In summary, erlotinib is orally available, generally well-tolerated, and has less impact on the quality of life.[23]

Clinical Studies and Efficacy

The concept of using erlotinib as maintenance therapy in NSCLC was a logical step, as it has shown an improvement in survival, delayed disease progression and delayed worsening of disease-related symptoms in the advanced NSCLC setting after progressing with previous chemotherapy.[16] This new class of agents has been investigated as maintenance therapy using two approaches (Table 1): immediate sequential therapy (IST) and prolonged response-dependent therapy (PRT) (Fig. 2). The IST approach consists of using an EGFR TKI immediately after completion of standard induction chemotherapy if the disease is stable or responding to initial chemotherapy. IST is based on the historic tumor growth model proposed by Goldie and Coldman,[24] in which sequential use of different agents could potentially evade the development of resistance in cancer cells. The PRT approach uses an EGFR TKI as front line therapy in conjunction with chemotherapy. If there is stable disease or response to the initial combination of an EGFR TKI with chemotherapy, the EGFR TKI is continued alone until disease progression.

Several studies have been done using these approaches and we will review them in detail. Although the INTACT 1,[25] INTACT 2,[26] TRIBUTE[27] and the TALENT trials[28] did not show any overall survival benefit with the addition of an EGFR TKI to platinum-based doublet regimens then followed by maintenance therapy in patients with chemotherapy-naïve advanced NSCLC, a subset analysis of the TRIBUTE trial showed that patients treated with erlotinib for more than 150 days showed an increased response duration, strengthening the suggestion of erlotinib in the maintenance setting. Similarly, in the INTACT 2 trial, patients with adenocarcinoma that received more than 90 days of 500 mg or 250 mg of gefitinib with chemotherapy followed by gefitinib at respective doses, had a longer median survival compared with patients treated with chemotherapy alone, 16 and 17 m vs. 13.9 m respectively.

Two trials evaluating immediate sequential therapy have shown a statistically significant improvement in OS, one involving an EGFR TKI.[29] Ciuleanu and colleagues investigated maintenance pemetrexed versus placebo in patients who had completed four cycles of platinum-based double-agent chemotherapy without evidence of disease progression.[29] Similar to Ciuleanu's trial methods above, the SATURN trial investigated maintenance erlotinib 150 mg/day compared with placebo in patients without disease progression after four cycles of a platinum-doublet.[30] Co-primary end-points were evaluated: Progression Free Survival (PFS) in the intent-to-treat patient population and PFS in the subset of patients with EGFR protein overexpression by immunohistochemistry, defined as $>10\%$. 1949 patients received induction platinum-based chemotherapy at the discretion of individual investigators (bevacizumab and pemetrexed were not permitted as the non-platinum agent); of the 45% of patients who had disease control after four cycles, 438 patients were randomized to erlotinib and 451 patients to placebo. Differences in PFS and OS (although a secondary endpoint) were in favor or erlotinib. The median PFS was 12.3 weeks for erlotinib compared to 11.1 weeks for placebo (HR 0.71, $P < 0.0001$) and overall survival showed a one-month survival advantage, 12 months compared to 11 months respectively (HR 0.81, $P = 0.0088$). Quality of life was also assessed using the validated Functional Assessment of Cancer Therapy—Lung,[31] and there was no significant difference for time to deterioration in quality of life for patients receiving erlotinib compared to placebo. This study led to the approval of erlotinib in April 2010 as first-line maintenance therapy for patients with locally advanced or metastatic NSCLC who had not progressed after initial platinum-based chemotherapy. Currently, erlotinib is

Table 1. Trials using EGFR TKI as PRT or IST.

Type of treatment strategy	Phase III Trials	Initial therapy	Maintenance therapy	No of patients	Median overall survival	Overall response	Median time to progression
PRT	INTACT 1[25]	Gemcitabine/cisplatin/ Placebo vs. Gemcitabine/Cisplatin Gefitinib 250 mg 500 mg	Placebo vs. Gefitinib 250 mg 500 mg	363 vs. 365 365	10.9 m vs. 9.9 m 9.9 m	47.2% vs. 51.2% 50.3%	6 m vs. 5.8 m 5.5 m
PRT	INTACT 2[26]	Paclitaxel/carboplatin/ placebo vs. Paclitaxel/carboplatin Gefitinib 250 mg 500 mg	Placebo vs. Gefitinib 250 mg 500 mg	345 vs. 345 347	9.9 m/13.9 m# vs. 9.8 m/17.1 m# 8.7 m/16.1 m#	28.7% vs. 30.4% 30%	5 m vs. 5.3 m 4.6 m
PRT	Gatzemeier et al[28] TALENT trial	Cisplatin/gemcitabine/ placebo vs. Cisplatin/gemcitabine/ erlotinib	Placebo vs. Erlotinib	586 pts vs. 586 pts	44.1 wks vs. 43 wks	29.9% vs. 31.5%	24.6 wks vs. 23.7 wks
PRT	Herbst et al[27] TRIBUTE trial	Carboplatin/paclitaxel/ placebo vs. Carboplatin/paclitaxel/ erlotinib	Placebo vs. Erlotinib	540 pts vs. 539 pts	10.5 m/10.1 m& vs. 10.6 m/22.5 m&	19.3% vs. 21.5%	4.9 m/4.3 m& vs. 5.1 m/6 m&
IST	Perol et al[33]	Cisplatin/gemcitabine	Gemcitabine vs. Erlotinib vs. Observation	154 pts and 155 pts vs. 155 pts	NR	NR	3.7 m or 2.8 m* vs. 2.1 m
IST	Cappuzzo et al, "SATURN"[30]	Platinum-based chemotherapy	Erlotinib vs. Observation	447 pts vs. 437 pts	NR	NR	12.3 wks* vs. 11.1 wks
IST	Kabbinavar et al, "ATLAS"[32]	Platinum-based chemotherapy with bevacizumab	Bevacizumab/ placebo vs. Bevacizumab/ erlotinib	768 pts	13.6 m vs. 14.4 m	NR	3.7 m vs. 4.8 m*

Notes: *Statistically significant; #subgroup of adenocarcinoma treated >90 days; &adenocarcinoma, never smokers.
Abbreviations: NR, Not Reported; m, months.

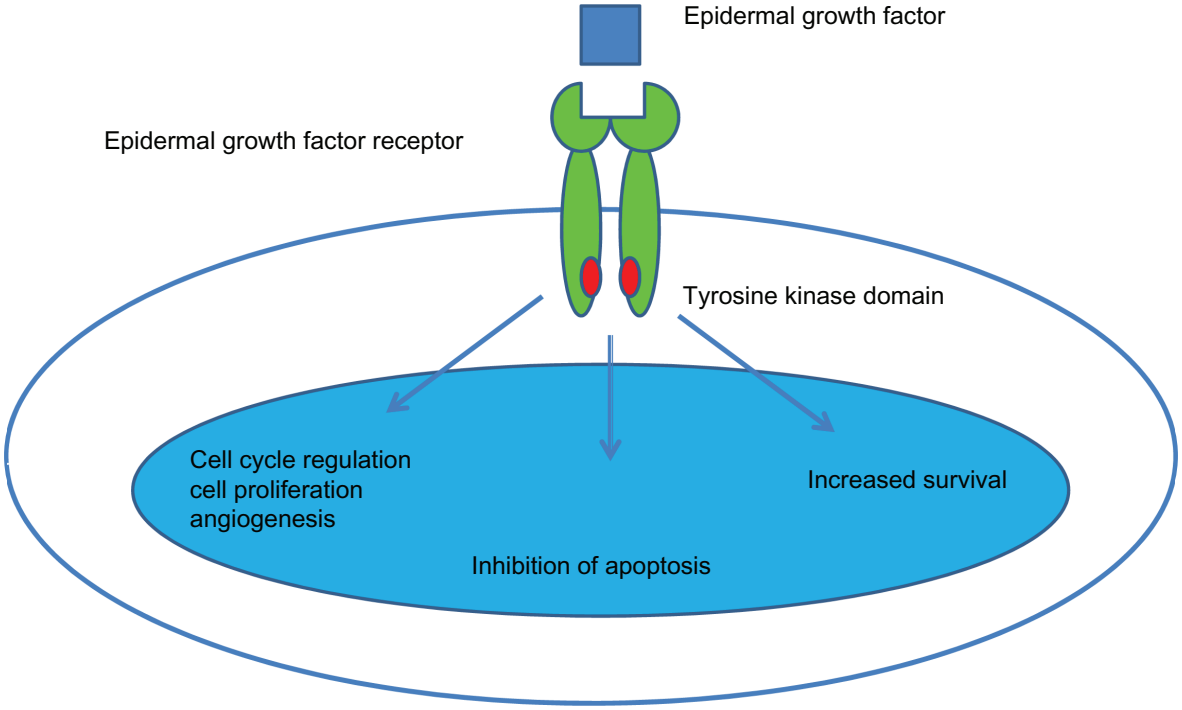

Figure 1. Representation of Epidermal Growth Factor Receptor in the surface of the cell and its biological effect on cellular processes. The tyrosine kinase domain represented in red is the target of EGFR TKI is located in the intracellular portion of the receptor and it is responsible for activation and phosphorylation of intracellular proteins. Adapted from Baselga J. *Cancer Cell*. 2002;2:93–5.

the only EGFR TKI approved by the US FDA for use in patients with NSCLC.

Since the introduction of bevacizumab in the initial therapy for non-small cell lung cancer, the ATLAS trial[32] sought to elucidate the efficacy of erlotinib with bevacizumab as IST. The study enrolled patients without disease progression after initial platinum-based therapy with bevacizumab and compared maintenance therapy with bevacizumab and erlotinib versus bevacizumab and placebo. The study met its primary endpoint after the second interim analysis showing improvement of PFS with the combination regimen versus bevacizumab alone (4.76 months compared to 3.71 months; HR = 0.71, $P = 0.0006$). However, the overall survival was not statistically different. A three-arm phase III trial investigating the role of maintenance gemcitabine or erlotinib compared with observation after initial therapy with cisplatin-gemcitabine looked at PFS as the primary endpoint.[33] Patients in both the gemcitabine arm and erlotinib arm experienced significantly longer progression-free survival when compared to the observation arm. Although gemcitabine and erlotinib were not compared head-to-head, median PFS was 3.8 months for the gemcitabine arm (n = 155 patients) and 2.9 months for the erlotinib arm (n = 155 patients). The data set is not mature yet, but no significant difference in overall survival has been observed at interim analyses. A pooled analysis of these 3 trials confirmed the benefit of maintenance therapy with EGFR TKI with improvement in OS (HR = 0.87; $P = 0.003$), and PFS (HR 0.76 ; $P < 0.00001$), All patients benefited from the therapy especially in the group of women non-smokers, non-squamous histology, PS 0 and patients who did not progress after 4 cycles of initial therapy.[34]

Discussion

Despite the disadvantage in research funding and less-than-robust grass-root movement for awareness of lung cancer in the community, there have been small yet significant advancements in the field of lung cancer therapy. The use of EGFR TKIs in NSCLC has proved beneficial in a variety of settings, yet this drug is just the beginning of a new wave of targeted therapies. The EGFR TKI is currently used routinely in the management of advanced lung cancer, but the setting of its use is in flux at the present time with several undefined issues.

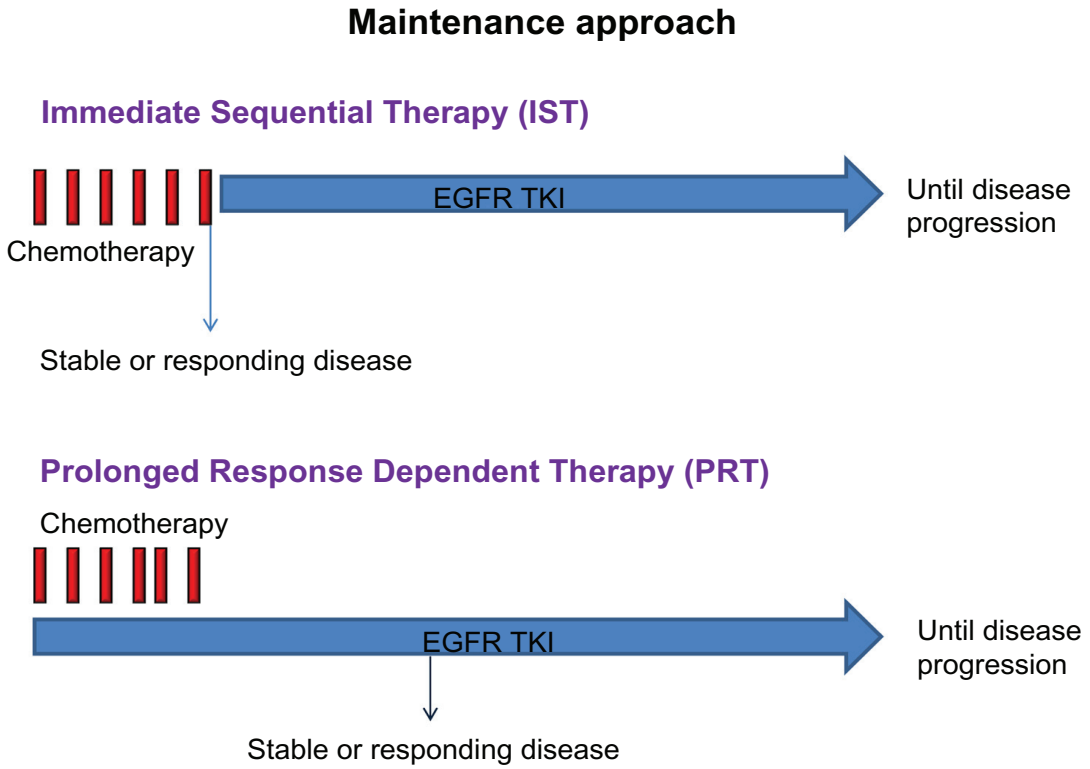

Figure 2. Two different approaches for maintenance therapy using EGFR TKIs. Immediate sequential therapy (IST) uses an EGFR TKI immediately after completion of standard induction chemotherapy if the disease is stable or responding to initial chemotherapy. The prolonged response dependent therapy (PRT) approach utilizes the EGFR TKI in first line therapy in conjunction with chemotherapy. If there is stable disease or response to the initial combination of an EGFR TKI with chemotherapy, the EGFR TKI is continued until disease progression.

The first issue is the timing in the use of erlotinib, especially in patients that harbors EGFR mutation. As early as 2006, phase II trials have looked into erlotinib as frontline therapy in advanced NSCLC,[35] even studying it exclusively in the elderly population over 70 years old.[36] The IPASS study was the first study to show the benefit of this class of drugs as a first line agent compared with chemotherapy in a population with favorable clinical characteristics as mentioned above. The study showed improved PFS in the subset of patients harboring an EGFR mutation.[37]

The next issue involves the expression of EGFR mutations. EGFR mutations are most commonly located on exon 19 or exon 21. The incidence of EGFR mutations in NSCLC varies from as low as 8% to as high as 66% of patients, depending on how the mutations are analyzed, geographical location, as Asia has higher frequency of mutations than North America, and other clinical characteristics.[38,39] Namely, EGFR mutations occur more frequently in females than males, are almost exclusively found in patients with adenocarcinoma histology (and nearly two times more likely in well-to moderately-differentiated adenocarcinomas than in poorly-differentiated adenocarcinomas), and are much more frequent in never-smokers than ever-smokers.[40,41] There appears to be an inverse correlation between smoke exposure and EGFR mutation, with higher amount of smoke exposure having lower incidence of EGFR mutation.[37,40] Not only does the EGFR mutation occur less often in smokers, but erlotinib is less effective in smokers due to lower serum levels as well. EGFR mutations do not seem to be associated with the age of the patient or stage of the lung cancer.[39] In 2004, when the FDA came out with their report on the aforementioned gefitinib, the exact same clinical characteristics were thought to be predictive of response to EGFR TKIs prior to the knowledge about of EGFR mutation.[15] The reason can now be explained; the patients with these clinical characteristics are most likely to harbor an EGFR mutation, who in turn respond best to EGFR TKIs.

Subsequent studies in Japan by Mitsudomi et al[42] and Maemondo et al[43] done exclusively in patients with EGFR mutation confirmed the improvement in response and PFS in patients with EGFR mutation

using gefitinib as first line therapy compared with chemotherapy. The OPTIMAL study,[38] a phase III trial, showed similar benefit using erlotinib in the first line setting. No trial has yet to show a statistically significant median overall survival benefit in the first line setting, although the Maemondo et al trial showed a 7 month survival advantage[42] (Table 2). As EGFR testing becomes more routine in clinical practice, erlotinib and other EGFR TKIs may soon become one of the standard agents used in first-line therapy for patients with EGFR mutation. In the near future, it would be plausible to see another FDA-approved indication for EGFR TKIs as first line therapy in NSCLC. This would alter the concept of IST maintenance after chemotherapy.

The third issue is the testing of tumors for the genetic mutation. Testing for mutations in EGFR, overexpression of EGFR protein levels via immunohistochemistry or an increase in gene copy numbers via fluorescence in-situ hybridization requires a non-neglible amount of tumor, which can be problematic when the majority of patients diagnosed with lung cancer had a fine needle aspiration or bronchoscopy washing. With the availability of an increasing number of specific molecularly-targeted agents, the acquisition of a predetermined amount of fresh tumor tissue for testing at time of initial diagnosis may become standard of care. Currently, the EGFR mutation analysis is the gold standard to determine if patients are likely to respond to erlotinib. As discussed previously, this is a time consuming method and it may not be available in patients with suboptimal tissue sampling. Other methods are currently available and others in the horizon will soon solve the dilemma of the need of additional biopsy in order to obtain tissue for testing.

Promising, cost-effective, and easy to sample, the matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry plasma proteomic signature (VeriStrat®)[44] appears to be able to predict those who will have improved PFS and OS with EGFR TKI therapy alone,[45] or in combination with the VEGF inhibitor, bevacizumab.[46] The results seem independent of histology, gender, ethnicity, smoking status, and other biomarkers like EGFR and *K-ras*. Carbone et al tested the serum from 441 of the 731 original patients from the BR.21 trial[16] and classified patients into VeriStrat Good (VSGood)

Table 2. First line therapy using EGFR TKIs vs. conventional chemotherapy in patients with advanced NSCLC.

Trial	Inclusion criteria	Therapy arms	No of patients	Median overall survival	Overall response	Median time to progression
Mok et al, "IPASS"[37] (Phase III)	Asian Age > 18 Adenocarcinoma or bronchioloalveolar carcinoma Non-smoker or former light smoker WHO PS 0–2	Gefitinib vs. Carboplatin + paclitaxel for up to 6 cycles	609 132* 91** vs. 608 129* 85**	18.8 m 21.6 m* 11.2 m** vs. 17.4 m 21.9 m* 12.7 m**	43% 71.2%* 1.1%** vs. 32.2% 47.3%* 23.5%**	5.7 m 9.6 m* 1.6 m** vs. 5.8 m 6.3 m* 5.5 m**
Mitsudomi et al[42] (Phase III)	Age ≤ 75 EGFR mutation + Included pts with post-op recurrent disease WHO PS 0–1	Gefitinib vs. Cisplatin + docetaxel every 21 days for 3–6 cycles	86 vs. 86	Not reported	62.1% vs. 32.2%	9.2 m vs. 6.3 m
Maemondo et al[43] (Phase III)	Age < 75 EGFR mutation + ECOG PS 0–2	Gefitinib vs. Carboplatin + paclitaxel for 3–6 cycles	114 vs. 114	30.5 m vs. 23.6 m	73.7% vs. 30.7%	10.8 m vs. 5.4 m
Zhou et al, "OPTIMAL"[39] (Phase III)	Age > 18 EGFR mutation + ECOG PS 0–2	Erlotinib vs. Carboplatin + gemcitabine for up to 6 cycles	82 vs. 72	Not reported	83% vs. 36%	13.1 m vs. 4.6 m

Notes: *Presence of EGFR mutation; **negative for EGFR mutation.

or VeriStrat Poor (VSPoor), with only 1% being indeterminately classified.[47] In the 292 of 441 patients who received erlotinib therapy in the second- or third-line setting, this test was predictive of disease control rate (VSGood: 68.2% vs. VSPoor: 30.5%; $P = 0.0001$) and objective response rate (VSGood: 11.5% vs. VSPoor: 1.0%; $P = 0.002$). Those patients classified as VSGood who received erlotinib (n = 183 patients) had a median overall survival of 10.5 months compared to the 4.0 month median overall survival in the remaining 109 patients who received erlotinib yet were classified as VSPoor. This was statistically significant, with a hazard ratio of 0.37 (95% CI: 0.28–0.48; $P < 0.0001$) favouring the erlotinib arm. A subsequent study showed that this test can also be used when erlotinib is combined with bevacizumab.[45] The median OS was 61 weeks in the group classified as "good" compared to 24 weeks in the "poor" group, and median PFS was 36 weeks compared to 8 weeks, respectively. Most recently, Lazzari and colleagues looked into the plasma proteomic profiles of 111 NSCLC patients at baseline, during the course of EGFR TKI therapy and at treatment withdrawal.[48] At baseline, a "good" classification by VeriStrat, when compared with those classified as "poor", correlated with longer PFS (HR 0.54, $P = 0.005$) and OS (HR 0.4, $P < 0.0001$), correlating with previous studies. About one-third of those classified as "good" at baseline had changed to "poor" predictive value at the time of treatment withdrawal, associated with the development of new cancerous lesions, suggesting its utility not only in treatment selection but possibly in treatment monitoring as well. Despite these positive studies, Taguchi et al[43] showed that VeriStrat does not appear to be prognostic for NSCLC patients not treated with EGFR TKI therapy, looking at three control groups from Italy, Vanderbilt and Poland; there was no statistically significant difference in risk of death between VSGood and VSPoor groups. These studies show that VeriStrat could be a valuable tool to predict response to therapy. As it is currently available, VeriStrat could alter the decision making in the use of erlotinib.

Detection of EGFR mutation in circulating lung cancer tumor cells is a feasible technique demonstrated in a study published in 2008.[49] Similar to the studies testing for the EGFR mutation in the tumor,[37–40] the patients with positive EGFR mutation detected in their circulating tumor cells showed improved outcome. If this is a concept that can be proven in a large scale study, the need for biopsy of the tumor for testing may became obsolete, eliminating the risks associated with these procedures.

The presence of a different mutation involving K-ras seems to confer decreased activity with EGFR TKIs.[50] This leads into another important question: is it still rational to use erlotinib in patients without knowledge of the EGFR expression/mutation or K-ras pathway? Due to the reliance on an adequate tissue sample, better predictive tools will guide and optimize future treatment strategies in NSCLC.

Ongoing studies are hoping to answer questions regarding the use of erlotinib in maintenance therapy for advanced NSCLC. Currently a study being conducted by Roche (NCT01328951) is investigating the role of IST with erlotinib versus erlotinib at time of progression. The primary endpoint is overall survival outcome and this study interestingly excludes all patients that harbor EGFR mutation. Another study is investigating the combination of erlotinib with OSI-906 (a IGF-1R, insulin growth factor-1 receptor tyrosine kinase inhibitor) versus erlotinib with placebo in patients with non-progressive disease after four cycles of platinum-based induction chemotherapy (NCT01186861) for advanced NSCLC.

Several new EGFR tyrosine kinase inhibitor like Lapatinib, BIBW 2992, and others are currently in clinical trials. If proven effective, they will be added to the number of agents currently available to treat lung cancer.

In conclusion, erlotinib is a well-tolerated oral EGFR TKI that currently has a role in maintenance therapy in NSCLC. Its use in lung cancer is already widely accepted, but our knowledge regarding when to use and in what circumstances will likely shift in the near future. The availability of more accessible techniques for mutational testing of EGFR and K-ras as well as improvement of laboratory testing will allow us to select the patient population that will benefit the most from these agents. This pharmaco-genetic selection will undoubtedly move us closer to the personalized medicine that the oncology field has set out to achieve since its inception, and that our patients have pleaded and hoped for decades.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal

and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

References

1. American Cancer Society Facts and Figures 2011.
2. http://www.nationallungcancerpartnership.org/lung-cancer-info/lung-cancer-research. Accessed October 10, 2011.
3. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355:2542–50.
4. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomized phase III trial. *Lancet*. 2009;373:1525–31.
5. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for non-squamous non-small-cell lung cancer: results from a randomized phase III trial (AVAIL). *Ann Oncol*. 2010;21:1804–9.
6. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cispltin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26:3543–51.
7. Lara PN Jr, Redman MW, Kelly K, et al. Disease control rate at 8 weeks predicts clinical benefit in advanced non-small-cell lung cancer: results from Southwest Oncology Group randomized trials. *J Clin Oncol*. 2008;26:463–7.
8. Park JO, Kim SW, Ahn JS, et al. Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non-small-cell lung cancer. *J Clin Oncol*. 2007;25:5233–9.
9. Socinski MA, Schell MJ, Peterman A, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. *J Clin Oncol*.2002;20:1335–43.
10. Barata F, Parente B, Teixeira E, et al. Optimal duration of chemotherapy in non-small-cell lung cancer: multicenter, randomized, prospective clinical trial comparing 4 vs. 6 cycles of carboplatin and gemcitabine. *J Thorac Oncol*. 2007;2:S666.
11. Smith IE, O'Brien ME, Talbot DC, et al. Duration of chemotherapy in advanced non-small-cell lung cancer: a randomized trial of three versus six courses of mitomycin, vinblastine, and cisplatin. *J Clin Oncol*. 2001;19:1336–43.
12. von Plessen C, Bergman B, Andresen O, et al. Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. *Br J Cancer*. 2006;95:966–73.
13. Kris MG, Natale RB, Herbst RS, et al. Efficacy of Gefitinib, an Inhibitor of the Epidermal Growth Factor Receptor Tyrosine Kinase, in Symptomatic Patients with Non-Small Cell Lung Cancer. *JAMA*. 2003;290:2149–58.
14. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomized, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet*. 2005;366:1527–37.
15. Cohen MH, Williams GA, Sridhara R, et al. Report from the FDA: United States Food and Drug Administration Drug Approval Summary: Gefitinib (ZD1839; Iressa) Tablets. *Clin Cancer Res*. 2004;10:1212–8.
16. Sheperd FA, Pereira JR, Ciuleanu T, et al. Erlotinib in Previously Treated Non-Small-Cell Lung Cancer. *N Engl J Med*. 2005;353:123–32.
17. Lynch TJ, Bell DW, Sordella R, et al. Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib. *N Engl J Med*. 2004;350:2129–39.
18. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304:1497–500.
19. Salomon DS, Brandt R, Ciardiello F, et al. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol*. 1995;19:183–232.
20. Hamilton M, Wolf JL, Rusk J, et al. Effects of Smoking on the Pharmacokinetics of Erlotinib. *Clin Cancer Res*. 2006;12:2166–71.
21. http://www.gene.com/gene/products/information/pdf/tarceva-prescribing.pdf. Accessed March 11, 2011.
22. Socinski MA, Morris DE, Masters GA, et al. Chemotherapeutic management of stage IV non-small cell lung cancer. *Chest*. 2003;123:226S–43.
23. Bezjak A, Tu D, Seymour L, et al. Symptom improvement in lung cancer patients treated with erlotinib: Quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group study BR.21. *J Clin Oncol*. 2006;25:3831–7.
24. Goldie JH, Coldman AJ, Gudauskas GA. Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treat Rep*. 1982;66:439–49.
25. Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in Combination with Gemcitabine and Cisplatin in Advanced Non-Small-Cell Lung Cancer: A Phase III Trial—INTACT 1. *J Clin Oncol*. 2004;22:777–84.
26 Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol*.2004;22:785–94.
27. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: A Phase III Trial of Erlotinib Hydrochloride (OSI-774) Combined with Carboplatin and Paclitaxel Chemotherapy in Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2005;23:5892–9.
28. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III Study of Erlotinib in Combination With Cisplatin and Gemcitabine in Advanced Non-Small-Cell Lung Cancer: The Tarceva Lung Cancer Investigation Trial. *J Clin Oncol*. 2007;25:1545–52.
29. Tudor Ciuleanu, Thomas Brodowicz, Christoph Zielinski, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *The Lancet*. October 24–30, 2009; 374(9699):1432–40.
30. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomized, placebo-controlled phase 3 study. *Lancet Oncol*. 2010;11:521–9.
31. Cella D, Bonomi A, Lloyd S, et al. Reliability and validity of the Functional Assessment of Cancer Therapy—Lung (FACT-L) quality of life instrument. *Lung Cancer*. 1995;12:199–200.
32. Kabbinavar FF, Miller VA, Johnson BE, et al. 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*. 2010;28 Suppl:Abstr 7526.
33. Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study. *J Clin Oncol*. 2010;28 Suppl: Abstr 7507.
34. Petrelli F, Borgonovo K, Cabiddu M, et al. Erlotinib as maintenance therapy in patients with advanced non-small cell lung cancer: a pooled analysis of three randomized trials. *Anticancer Drugs*. 2011;22:1010–9.
35. Giaccone G, Gallegos Ruiz M, Le Chevalier T, et al. Erlotinib for frontline treatment of advanced non-small cell lung cancer: a phase II study. *Clin Cancer Res*. 2006;12:6049–55.

36. Jackman DM, Yeap BY, Lindeman NI, et al. Phase II clinical trial of chemotherapy-naïve patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. *J Clin Oncol*. 2007;25:760–6.
37. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma. *N Engl J Med*. 2009;361:947–57.
38. Pham DK, Kris MG, Riely GJ, et al. Use of Cigarette-Smoking History to Estimate the Likelihood of Mutations in Epidermal Growth Factor Receptor Gene Exons 19 and 21 in Lung Adenocarcinomas. *J Clin Oncol*. 2006;24: 1700–4.
39. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomized, phase 3 study. *Lancet Oncol*. 2011;12:735–42.
40. Kosaka T, Yatabe Y, Endoh H, et al. Mutations of the Epidermal Growth Factor Receptor Gene in Lung Cancer: Biological and Clinical Implications. *Cancer Res*. 2004;64;8919–23.
41. Matsuo K, Ito H, Yatabe Y, et al. Risk factors differ for non-small-cell lung cancers with and without EGFR mutation: assessment of smoking and sex by a case-control study in Japanese. *Cancer Science*. 2007;98:96–101.
42. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomized phase 3 trial. *Lancet Oncol*. 2010;11:121–8.
43. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or Chemotherapy for Non-Small-Cell Lung Cancer with Mutated EGFR. *N Engl J Med*. 2010; 362:2380–8.
44. Taguchi F, Solomon B, Gregorc V, et al. Mass spectrometry to classify non-small-cell lung cancer patients for clinical outcome after treatment with epidermal growth factor receptor tyrosine kinase inhibitors: multicohort cross-institutional study. *J Natl Cancer Inst*. 2007;99:838–46.
45. Salmon JS, Chen H, Chen S, et al. Classification by mass spectrometry can accurately and reliably predict outcome in patients with non-small cell lung cancer treated with erlotinib-containing regimen. *J Thorac Oncol*. 2009;4: 689–96.
46. Carbone DP, Salmon JS, Billheimer D, et al. VeriStrat classifier for survival and time to progression in non-small-cell lung cancer (NSCLC) patients treated with erlotinib and bevacizumab. *Lung Cancer*. 2010;69:337–40.
47. Carbone DP, Seymour L, Ding K, et al. Serum Proteomic Prediction of Outcomes in Advanced NSCLC Patients Treated with Erlotinib/Placebo in the NCIC Clinical Trials Group BR.21 Trial. *J Thorac Oncol*. 2010; 5 Suppl:Abstr 203O.
48. Lazzari C, Spreafico A, Bachi A, et al. Changes in Plasma Mass-Spectral Profile in Course of Treatment of Non-small Cell Lung Cancer Patients with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors. *J Thorac Oncol*. September 29, 2011. [Epub ahead of print.]
49. Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in EGFR in circulating lung-cancer cells. *N Engl J Med*. 2008;359:366–77.
50. Roberts PJ, Stinchcombe TE, Der CJ, et al. Personalized Medicine in Non-Small-Cell Lung Cancer: Is KRAS a Useful Marker in Selecting Patients for Epidermal Growth Factor Receptor-Targeted Therapy? *J Clin Oncol*. 2010;28:4769–77.

Supplementary Data

A video abstract by the authors of this paper is available. video-abstract5127.mov