Review Article

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for Elderly Patients with Advanced Non-Small Cell Lung Cancer

F. Meriggi and A. Zaniboni

Oncology Department, Fondazione Poliambulanza, 25124 Brescia, Italy

Correspondence should be addressed to A. Zaniboni, zanib@numerica.it

Received 31 August 2009; Revised 14 March 2010; Accepted 7 April 2010

Academic Editor: Alexander Bürkle

Lung cancer is the leading cause of cancer-related mortality in both men and women and approximately 219,440 new cases of nonsmall cell lung cancer (NSCLC) were estimated to occur in the USA in 2009, which caused 159,390 NSCLC-related deaths. More than 50% of cases of advanced NSCLC are diagnosed in patients older than age 65, and recent Surveillance Epidemiology and End Results (SEERs) data suggest that the median age at diagnosis is 70 years. Until recently, the disease has been undertreated in this patient population, with a perception among many clinicians that elderly patients do not tolerate chemotherapy or radiotherapy. So, single agent chemotherapy is the recommended approach by the ASCO and International Expert Panels in unselected patients. The introduction of novel targeted therapies, such as Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors (TKIs) which improved survival versus placebo in patients who had previously failed on chemotherapy, gives clinicians new, effective, and better tolerated options to consider when treating NSCLC in elderly patients. This paper describes the advances of EGFR TKIs for elderly patients with advanced NSCLC.

1. Introduction

Lung Cancer is the most common cancer in the world and the leading cause of cancer-related deaths in Western countries [1]. NSCLC constitutes between 80% and 85% of all lung cancers. The median age at diagnosis is now 70 years [2] and most patients with NSCLC have incurable disease at diagnosis, with only approximately 15% presenting with localized disease [3]. Treatment for advanced disease is palliative in nature. In patients with a good performance status (PS), first-line treatment with platinum-based combination chemotherapy leads to improved overall survival (OS) and improvement in symptoms [4–6]. However, in elderly patients, single-agent chemotherapy with a third-generation agent (vinorelbine, gemcitabine, or taxanes) is the recommended approach by the American Society of Clinical Oncology guidelines and international expert panels in unselected patients [7, 8]. Moreover, in current practice, the elderly are often excluded from participation in clinical trials and receive empirical or inadequate treatment [9]. Retrospective analyses of trials not restricted to elderly patients have generally demonstrated that the elderly have similar response rates (RRs) to chemotherapy as younger patients and also similar survival benefits. Most studies also have shown that older patients are more likely to stop treatment as a result of toxicity, although, objectively, these studies have reported either little or no increase in toxicity in elderly subgroup [8, 10–16]. Availability of an effective, less toxic therapy might help extend potentially beneficial treatment to a greater proportion of older patients with advanced NSCLC and TKIs represent just these kinds of drugs. The EGFR family is part of a complex signal-transduction network that is central to several critical cellular processes. The EGFR (also known as ErbB-1/HER1) is a 170-kDa transmembrane glycoprotein that consists of an extracellular domain that recognizes and binds to specific ligands, a hydrophobic transmembrane domain, which is involved in interactions between two receptors within the cell membrane, and an intracellular domain that contains the tyrosine kinase enzymatic activity. Since EGFR expression is often found in NSCLC cells [17, 18], it has been the focus of efforts to develop new agents that target the
EGFR pathway. Erlotinib and gefitinib inhibit the tyrosine kinase activity of EGFR and have been studied extensively [19–22]. Besides the two rather selective TKIs of EGFR, other TKIs with a broader spectrum of activity and other Monoclonal Antibodies (MoAb) to extracellular domain of the EGFR are also being tested in advanced NSCLC. Among broader spectrum EGFR TKIs are lapatinib, which are also active against ErbB2/neu, another member of the EGFR family of receptors, and vandetanib, which inhibits the Vascular Endothelial Growth Factor (VEGF) receptor [23]. However, lapatinib is approved for the treatment of advanced breast cancer and the development of vandetanib has been discontinued by AstraZeneca in 2010.

2. Gefitinib

Gefitinib (ZD1839) is an orally available EGFR small-molecule TKI. In two large phase II trials, IDEAL 1 and 2, gefitinib monotherapy was demonstrated to be active and well tolerated in advanced NSCLC patients which progressed after one or more chemotherapy regimens [20, 21]. These trials led to US FDA approval of gefitinib as salvage third-line therapy for NSCLC in May 2003, as a single agent after failure of both platinum-based and docetaxel chemotherapies. Gefitinib activity as a single agent at a dose of 250 mg was not confirmed in a placebo controlled randomized phase III Iressa Survival Evaluation in Lung Cancer (ISEL) trial in advanced NSCLC with heavily pretreated patients [24]. However, preplanned subgroup analyses indicated statistically different survival benefit in never smokers and in patients of Eastern Asian origin. In June 2005, on the basis of the lack of survival benefit in the ISEL study, the FDA restricted the use of gefitinib to patients participating in a clinical trial or who were continuing to benefit from treatment already initiated [25]. Currently, gefitinib is marketed in several countries in eastern Asia and in the late 2009 was approved by EMEA for the treatment of locally advanced or metastatic NSCLC patients who have been pretreated with platinum-based chemotherapy.

Two further studies retrospectively analyzed gefitinib in previously treated elderly patients with advanced NSCLC and reported a response rate of 0% and 5%, respectively. However, in the Cappuzzo et al. study, the stable disease rate was 45% [26, 27].

Recently, the INTEREST-randomized phase III trial in previously treated NSCLC established noninferior survival of gefitinib compared with docetaxel (7.6 versus 8.0 months, resp.), suggesting that gefitinib is a valid treatment for pretreated patients with advanced NSCLC. Superiority of gefitinib in patients with high EGFR-gene-copy number was not proven [28]. In our knowledge, the only published paper on gefitinib as first-line treatment and elderly patients with advanced NSCLC was published by Crinò et al. [29]. They performed a randomized phase II study (INVITE) of gefitinib versus vinorelbine in 196 chemotherapy-naïve unselected elderly patients (age ≥70 years). Patients enrolled in this study reflected a European population seen in clinical practice, because the vast majority of patients were male (77%), were smokers (82%), and had squamous cell carcinoma (48%). The primary end point was progression-free survival (PFS). Secondary end points were overall survival (OS), objective response rate (ORR), quality of life (QoL), pulmonary symptom improvement (PSI), and tolerability. This study showed no statistical difference between gefitinib and vinorelbine in terms of PFS (2.7 versus 2.9 months, resp. \( P = .310 \)), OS (5.9 versus 8.0 months, resp.), ORR (3.1% versus 5.1%, resp.), and disease control rates (43.3% versus 53.5%, resp.); however, the toxicity profile and overall QoL assessments favored gefitinib. Drug-related serious adverse events (AEs) were less frequent in the gefitinib arm versus vinorelbine arm (12.8% versus 41.7%, resp.). Patients treated with gefitinib had a numerically lower incidence of fatigue and gastrointestinal AEs, notably constipation, which is an important side effect in the elderly population and also hematologic toxicity was confined to patients treated with vinorelbine. Most patients were analyzed for EGFR gene copy number by FISH, and surprisingly, those who were EGFR FISH-positive and who received gefitinib appeared to have poorer outcomes than those who were EGFR FISH-negative and who received gefitinib. In the small subgroup of EGFR FISH-positive patients, those treated with vinorelbine achieved nonsignificant better PFS and OS than those treated with gefitinib. A clear explanation for the discrepancy in FISH result is not currently evident, but it could be useful to perform EGFR as well K-RAS mutation analyses in this patient population. Unfortunately, in INVITE trial there were too few patients in the K-RAS mutation analysis to draw any accurate conclusions [29] (Table 1).

The first-line gefitinib versus carboplatin/paclitaxel (Iressa Pan-Asia Study (IPASS) study was a phase III study in clinically selected patients in East Asia who had advanced NSCLC. The primary end point was PFS and evaluations of efficacy according to the baseline biomarker status of EGFR were planned exploratory objectives. There was a significant interaction between treatment and EGFR mutation with respect to PFS (\( P < .001 \)). PFS was significantly longer among patients receiving gefitinib than that among those receiving carboplatin-paclitaxel in the mutation-positive subgroup (\( P < .001 \)) and significantly shorter among patients receiving gefitinib than that among receiving carboplatin-paclitaxel in the mutation-negative subgroup (\( P < .001 \)). The ORR in the overall population was significantly higher with gefitinib than that with carboplatin-paclitaxel (43% versus 32.2%, resp.; \( P < .001 \)). The ORR was 71.2% with gefitinib versus 47.3% with carboplatin-paclitaxel in the mutation-positive subgroup (\( P < .001 \)) and 1.1% versus 23.5%, respectively, in the mutation-negative subgroup (\( P = .001 \)). Significantly more patients in the gefitinib group than in the carboplatin-paclitaxel group had a clinically relevant improvement in quality of life (\( P < .001 \)). Interstitial lung disease (ILD) events occurred in 2.6% patients treated with gefitinib and in 1.4% patients treated with carboplatin-paclitaxel. The Authors concluded that gefitinib is superior to carboplatin-paclitaxel as an initial treatment for pulmonary adenocarcinoma among nonsmokers or former light smokers in East Asia. The presence in the tumor of a mutation of the EGFR gene is
Toxicity (grade ≥3) was more frequent in the elderly group than in the younger group (3.0 months versus 2.1 months, resp.) and in survival benefit between the elderly subgroup enrolled in BR.21 study and demonstrated similar survival and QoL benefits as younger counterpart when single-agent erlotinib in 81 unselected chemotherapy-naïve patients with advanced NSCLC and a PS of 2. The overall control disease rate was 42% and the median survival of patients with possible ILD, with one treatment-related death. Median time to progression (TTP) was 3.5 months and median survival time was 10.9 months. The 1- and 2-year survival rates were 46% and 19%, respectively. Treatment-related rash was correlated with prolonged TTP and survival, while smoking history and weight loss at presentation were predictors of shorter survival. The presence of an EGFR mutation was strongly correlated with disease control, prolonged TTP (P < .017) and survival (P < .027). Not surprisingly, patients with a KRAS mutation had no clinical responses and a median TTP of only 2.5 months. Finally, tumor histology (64% of patients had adenocarcinoma) was not associated with improved survival in this trial [33] (Table 1). Hesketh et al. published the results of phase II study that evaluated the efficacy and tolerability of single-agent erlotinib in 81 unselected chemotherapy-naïve patients with advanced NSCLC and a PS of 2. The median age of enrolled patients was 74 years. The overall control disease rate was 42% and the median survival of 5 months is comparable with that reported in prior trials employing chemotherapy alone in the PS 2 population [34–38]. This SWOG trial demonstrated that single-agent erlotinib resulted in an acceptable but significant level of treatment-related side effects for a substantial minority of chemotherapy-naïve patients with advanced NSCLC and PS 2. Moreover, erlotinib does not offer a significant treatment advance over chemotherapy in unselected PS 2 patients [38]. Lilienbaum et al. confirmed that unselected patients with advanced NSCLC and PS 2 are best treated with combination chemotherapy as first-line therapy. However, erlotinib may be considered in patients selected by clinical or molecular markers [37].

A recent phase II study by Jackman et al. reported the efficacy of erlotinib as first-line treatment in 80 unselected patients greater than 70 years of age with stage IIB or IV NSCLC. There were eight partial responses and thirty-three stable diseases for an overall disease control rate of 51%. The most frequent AEs were rash (79%) and diarrhea (69%). In general, toxicities were mild and easily managed. Fifteen patients experienced treatment-related toxicities ≥grade 3. Twelve patients were removed from the protocol because of erlotinib-related toxicity (three patients with ILD, three with dehydration, three with diarrhea, one with hemoptysis, one with rash, and one with anorexia). There were four patients with possible ILD, with one treatment-related death. Median time to progression (TTP) was 3.5 months and median survival time was 10.9 months. The 1- and 2-year survival rates were 46% and 19%, respectively. Treatment-related rash was correlated with prolonged TTP and survival, while smoking history and weight loss at presentation were predictors of shorter survival. The presence of an EGFR mutation was strongly correlated with disease control, prolonged TTP (P < .017) and survival (P < .027). Not surprisingly, patients with a KRAS mutation had no clinical responses and a median TTP of only 2.5 months. Finally, tumor histology (64% of patients had adenocarcinoma) was not associated with improved survival in this trial [33] (Table 1). Hesketh et al. published the results of phase II study that evaluated the efficacy and tolerability of single-agent erlotinib in 81 unselected chemotherapy-naïve patients with advanced NSCLC and a PS of 2. The median age of enrolled patients was 74 years. The overall control disease rate was 42% and the median survival of 5 months is comparable with that reported in prior trials employing chemotherapy alone in the PS 2 population [34–38]. This SWOG trial demonstrated that single-agent erlotinib resulted in an acceptable but significant level of treatment-related side effects for a substantial minority of chemotherapy-naïve patients with advanced NSCLC and PS 2. Moreover, erlotinib does not offer a significant treatment advance over chemotherapy in unselected PS 2 patients [38]. Lilienbaum et al. confirmed that unselected patients with advanced NSCLC and PS 2 are best treated with combination chemotherapy as first-line therapy. However, erlotinib may be considered in patients selected by clinical or molecular markers [37].

A new paradigm of utilizing TKIs is as maintenance drug after first-line treatment obtaining control disease as recently shown in SATURN and ATLAS studies. The SATURN trial investigated the role of maintenance therapy with erlotinib in EGFR IHC-positive patients. Erlotinib significantly increased PFS (P = .000003) and overall survival from 11 months to 12 months compared with placebo [39]. In ATLAS trial, an improvement in PFS was obtained with the combination of erlotinib and bevacizumab versus bevacizumab and placebo as a maintenance therapy [40]. Moreover, in TORCH trial, Gridelli et al. are investigating whether erlotinib as first-line therapy until progression followed by chemotherapy with cisplatin/gemcitabine will not be inferior in terms

---

**Table 1: Main studies on EGFR TKIs for elderly (≥70 years) patients with advanced NSCLC.**

| Author               | Study arm            | No. of patients | Response rate (%) | Median OS (months) |
|----------------------|----------------------|-----------------|-------------------|--------------------|
| Shepherd* et al. [31]| Erlotinib versus     | 112             | 8                 | 7.6                |
|                      | Placebo              | 50              | 0                 | 5.0                |
| Wheatley-Price* et al. [32]| Erlotinib   | 80              | 10                | 10.9               |
| Crino* et al. [29]   | Gefitinib versus     | 99              | 3.1               | 5.9                |
|                      | Vinorelbine          | 97              | 5.1               | 8.0                |

*2nd or 3rd-line; § first-line.

---

...a strong predictor of a better outcome with gefitinib. This study was not targeted for elderly NSCLC patients (median age of enrolled patients was 57 years); however it showed that patients in whom an EGFR mutation has been identified will benefit most from first-line therapy with gefitinib [30].

### 3. Erlotinib

Erlotinib in a phase III, randomized, placebo-controlled trial (BR.21 study) has been proven to prolong survival compared with best supportive care (6.7 months versus 4.7 months for erlotinib and for placebo, resp.) in unselected NSCLC patients after first- or second-line chemotherapy failure [31]. Based on the results of this trial, erlotinib was approved by the US FDA in November 2004 and by the EMEA in October 2005 for the treatment of chemotherapy-resistant advanced NSCLC patients. However, the mild safety profile of erlotinib makes it particularly suitable to be tested prospectively as a single agent in the first-line treatment of elderly patients as an alternative to cytotoxic chemotherapy.

Wheatley-Price et al. performed a retrospective analysis of elderly subgroup enrolled in BR.21 study and demonstrated that elderly patients treated with erlotinib gain similar survival and QoL benefits as younger counterpart but experience greater toxicity. At study entry, 162 patients (22%) were pretreated elderly (112 randomly assigned to erlotinib). Eight percent of elderly erlotinib patients had an objective response, and 70% had a best response of stable disease compared with 9% and 59% of young patients, but these differences were not significant. No significant differences were seen in median duration of response (39 weeks versus 34 weeks, resp.) and in survival benefit between elderly and young patients (3.0 months versus 2.1 months, resp.). Thirty-five % of the elderly group experienced severe toxicity (grade ≥3) compared with 18% of the younger group (P < .001). The elderly were more likely than the younger group to have grade ≥3 rash, fatigue, stomatitis, and dehydration, as well as any grade of anorexia and fatigue. Fatal drug-related toxicities were unusual and occurred in only five patients (two young and three elderly patients).

When we consider dyspnea, cough, and pain, QoL benefits were similar in elderly and young patients [32] (Table 1).
of survival to the standard arm, consisting of first-line cisplatin/gemcitabine for 6 cycles, followed at progression by erlotinib until second progression [41].

4. Clinical and Molecular Predictors for Response to EGFR TKIs

Clinical data suggest that EGFR TKIs gefitinib and erlotinib are more active in certain NSCLC histotypes, such as in adenocarcinomas and bronchioloalveolar carcinomas (BAC), in women, in never smokers and in Asian ethnicity [30, 31, 42–46]. However, in BR.21 trial, survival was significantly improved in all subgroups of patients receiving erlotinib versus placebo, such as male smokers with squamous cell carcinoma [31]. A subgroup analysis of the TRIBUTE trial showed that the addition of erlotinib to paclitaxel/carboplatin prolonged survival in patients who never smoked (median survival 22.5 versus 10.1 months, \( P = .01 \)) [47]. Skin rash is a common adverse effect observed in all clinical trials with EGFR-targeting agents. The incidence of rash was higher with erlotinib than gefitinib [48] and may be due to the lower plasma concentration of gefitinib compared with erlotinib when administered at the recommended dosages of 250 and 150 mg/day, respectively. A correlation between the severity of skin rash (grade \( \geq 2 \)) and significant improvement of survival was observed in several clinical trials [49–51], and therefore, skin rash seemed to function as a surrogate marker of efficacy [51].

Somatic mutations in the EGFR gene are most frequently detected in NSCLC patients with a better outcome, including adenocarcinomas histology, in particular BAC, nonsmokers, females, and Asian ethnicity [37, 52, 53]. The most common mutations of EGFR are in a frame deletion in exon 19 (45%–50% of all somatic EGFR mutations) and a missense mutation leading to leucine to arginine substitution at codon 858 (L858R) in exon 21 (35%–45% of mutations) [54]. Emerging data suggest that patients with NSCLC and EGFR exon 19 deletion have a longer survival following treatment with gefitinib or erlotinib compared with those with L858R mutation [55–57]. Recently, IPASS study showed that, in the subgroup of 261 patients who were positive for the EGFR mutation, PFS was significantly longer among those receiving gefitinib than among those receiving carboplatin-paclitaxel as first-line treatment \( (P < .001) \) [37]. Several retrospective analyses of clinical trials have failed to demonstrate the correlation between EGFR IHC status and response, TTP and OS in NSCLC patients treated with gefitinib or erlotinib [58–62]. Conversely, in other clinical trials, it has been shown that high levels of EGFR protein expression are associated with response and improvement of survival [63–66]. Of note, EGFR FISH-positive status was significantly associated with certain clinical and biological characteristics predictive for TKI sensitivity, such as female sex, never-smoking history, and the presence of EGFR mutations [25]. However, the most predictive marker of response remains EGFR mutation/deletion status in the kinase domain.

In approximately 15%–30% of lung adenocarcinomas, activating mutations in the RAS family member were found. This more commonly occurs in patients with smoking history and these mutations are most frequently recorded in codons 12 and 13 in exon 2 of the K-RAS gene [67–69]. The role of K-RAS mutation in NSCLC patients is still controversial, but it seems associated with a worse outcome and a shorter survival [70].

5. Discussion

Treatment of elderly patients who have NSCLC remains a challenge. Older adults represent a heterogeneous population, despite similar chronologic age. Individualizing treatment decision-making based on careful patient assessment is currently an active area of research in geriatric oncology and will hopefully lead to improved treatment outcomes for older adults. These patients have more comorbidities and tend to be more intolerant of toxic medical treatment than their younger counterparts [71]. A comprehensive geriatric assessment (CGA), which has proven to provide more indications compared with the performance status assessment alone, ought to be carried out. The CGA should include evaluation of comorbidities, socioeconomic issues, nutritional status, polypharmacy, functional dependence, emotional and cognitive conditions, an estimate of life expectancy, and recognition of frailty. Nevertheless, a CGA may be too lengthy in busy clinical practice; so, validated and shorter screening instruments are needed. The Cardiovascular Health Study divided elderly patients into three groups (fit, prefrail, frail) according to five items (unintentional weight loss, self-reported exhaustion, weakness, walking speed, and level of physical activity) and has gained particular prominence because it is well correlated with mortality and risk of functional dependence [72, 73]. However, actually CGA remains the best option to decide on the best-suited treatment modality for a particular geriatric patient. Based on prospective trials for unselected elderly advanced NSCLC, single-agent chemotherapy with third-generation agents (vinorelbine, gemcitabine, taxanes) is still considered the recommended treatment.

Among targeted therapies, the EGFR TKIs, erlotinib and gefitinib are the most promising agents and have been shown in phase II trials to be active and well tolerated as first-line treatment of advanced NSCLC in the elderly. In responders to EGFR TKIs, the symptom relief was dramatically obtained also in PS \( \geq 2 \) patients [74–76]. Of note, most patients at the time of recurrence of NSCLC have suffered some types of toxicity from previous chemotherapy or comorbidities such as chronic renal failure, contraindicating any further chemotherapy. In a Gridelli et al. report, erlotinib at full dosage was administered to three advanced NSCLC patients unsuitable for chemotherapy because of chronic renal failure. Further renal function was not impaired by therapy with erlotinib, and no severe toxicity was recorded. Erlotinib is metabolized in the liver, mainly by the cytochrome p-450 isoenzyme CYP 3A4. Erlotinib and its metabolites are excreted predominantly via feces, with renal elimination.
of drug and metabolites accounting for less than 9% of the administered dose [77]. With interest are awaited the results of the GEST phase II study, where elderly patients with untreated advanced NSCLC were randomized to receive sorafenib plus gemcitabine or sorafenib plus erlotinib [78]. Another study currently ongoing is the ZELIG phase II randomized study with vandetanib plus gemcitabine versus gemcitabine alone in the same subset of elderly patients.

Finally, elderly patients with advanced NSCLC and carriers of an EGFR mutation may be considered for gefitinib or erlotinib as first-line treatment. However, further specifically designed phase III randomized trials are needed to optimize medical treatment of elderly patients with advanced NSCLC.

References

[1] D. M. Parkin, F. Bray, J. Ferlay, and P. Pisani, “Global cancer statistics, 2002,” CA: A Cancer Journal for Clinicians, vol. 55, no. 2, pp. 74–108, 2005.
[2] M. J. Hayat, N. Howlader, M. E. Reichman, and B. K. Edwards, “Cancer statistics, trends, and multiple primary cancer analyses from the surveillance, epidemiology, and end results (SEER) program,” Oncologist, vol. 12, no. 1, pp. 20–37, 2007.
[3] National Cancer Institute, “SEER stage distribution by race, sex and age group for lung and bronchus cancer: SEER 9 Registries for 1988–2003,” http://seer.cancer.gov/faststats/index.php?site=Lung_and_&%2520Bronchus_Cancer&stat_Survival.
[4] Non-Small Cell Lung Cancer Collaborative Group, “Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials,” British Medical Journal, vol. 311, no. 7010, pp. 899–909, 1995.
[5] K. Kelly, J. Crowley, P. A. Bunn Jr., et al., “Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial,” Journal of Clinical Oncology, vol. 19, no. 13, pp. 3210–3218, 2001.
[6] J. H. Schiller, D. Harrington, C. P. Belani, et al., “Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer,” The New England Journal of Medicine, vol. 346, no. 2, pp. 92–98, 2002.
[7] D. G. Pister, D. H. Johnson, C. G. Azzoli, et al., “American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003,” Journal of Clinical Oncology, vol. 22, no. 2, pp. 330–353, 2004.
[8] C. Gridelli, M. Aapro, A. Ardizzoni, et al., “Treatment of advanced non-small-cell lung cancer in the elderly: results of an international expert panel,” Journal of Clinical Oncology, vol. 23, pp. 3125–3137, 2005.
[9] J. H. Lewis, M. L. Kilgore, D. P. Goldman, et al., “Participation of patients 65 years of age or older in cancer clinical trials,” Journal of Clinical Oncology, vol. 21, no. 7, pp. 1383–1389, 2003.
[10] F. V. Fossella and C. Belani, “Phase III study (TAX 326) of docetaxel-cisplatin (DC) and docetaxel-carboplatin (DCb) versus vinorelbine-cisplatin (VC) for the first line treatment of advanced/metastatic non-small-cell lung cancer (NSCLC): analyses in elderly patients,” Proceedings of the American Society of Clinical Oncology, vol. 22, p. 629a, 2003, abstract no. 2528.
[11] K. Kelly, S. Giarritta, W. Akerley, et al., “Should older patients (Pts) receive combination chemotherapy for advanced stage non-small cell lung cancer (NSCLC)? An analysis of Southwest Oncology trials 9509 and 9308,” Proceedings of the American Society of Clinical Oncology, vol. 20, p. 329a, 2001, abstract no. 1313.
[12] C. Langer, M. Vangel, J. Schiller, et al., “Age-specific subanalysis of ECOG 1594: fit elderly patients (70–80 YRS) with NSCLC do as well as younger pts (<70),” Proceedings of the American Society of Clinical Oncology, vol. 22, p. 639a, 2003, abstract no. 2571.
[13] C. Gridelli and F. A. Shepherd, “Chemotherapy for elderly patients with non-small cell lung cancer: a review of the evidence,” Chest, vol. 128, no. 2, pp. 947–957, 2005.
[14] C. J. Langer, J. Manola, P. Bernardo, et al., “Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of eastern cooperative oncology group 5592, a randomized trial,” Journal of the National Cancer Institute, vol. 94, no. 3, pp. 173–181, 2002.
[15] P. A. Bunn Jr. and R. Lilienbaum, “Chemotherapy for elderly patients with advanced non-small-cell lung cancer,” Journal of the National Cancer Institute, vol. 95, no. 5, pp. 341–343, 2003.
[16] T. Asmis, K. Ding, E. Shepherd, et al., “Are age and comorbidity prognostic factors in the treatment of metastatic non-small cell lung cancer (NSCLC): a review of a National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) randomized trial,” Lung Cancer, vol. 49, supplement 176, p. S85, 2005.
[17] V. Rusch, D. Klimstra, E. Venkatraman, P. W. T. Pisters, J. Langenfeld, and E. Dmitrovsky, “Overexpression of the epidermal growth factor receptor and its ligand transforming growth factor α is frequent in resectable non-small cell lung cancer but does not predict tumor progression,” Clinical Cancer Research, vol. 3, no. 4, pp. 515–522, 1997.
[18] J. Brabender, K. D. Danenberg, R. Metzger, et al., “Epidermal growth factor receptor and HER2-neu mRNA expression in non-small cell lung cancer is correlated with survival,” Clinical Cancer Research, vol. 7, no. 7, pp. 1850–1855, 2001.
[19] S. S. Sridhar, L. Seymour, and F. A. Shepherd, “Inhibitors of epidermal-growth-factor receptors: a review of clinical research with a focus on non-small-cell lung cancer,” Lancet Oncology, vol. 4, no. 7, pp. 397–406, 2003.
[20] M. Fukuoka, S. Yano, G. Giaccone, et al., “Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (the IDEAL trial),” Journal of Clinical Oncology, vol. 21, no. 12, pp. 2237–2246, 2003, Erratum in: Journal of Clinical Oncology, vol. 22, p. 4811, 2004.
[21] M. G. Kris, R. B. Natale, R. S. Herbst, et al., “Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial,” Journal of the American Medical Association, vol. 290, no. 16, pp. 2149–2158, 2003.
[22] R. Pérez-Soler, A. Chachoua, L. A. Hammond, et al., “Determinants of tumor response and survival with erlotinib in patients with non-small–cell lung cancer,” Journal of Clinical Oncology, vol. 22, no. 16, pp. 3238–3247, 2004.
[23] G. Giaccone, “Epidermal growth factor receptor inhibitors in the treatment of non-small-cell lung cancer,” Journal of Clinical Oncology, vol. 23, no. 14, pp. 3235–3242, 2005.
[24] N. Thatcher, A. Chang, P. Parikh, et al., “Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa...
in patients with advanced non-small-cell lung cancer and a performance status of 2," *Journal of Thoracic Oncology*, vol. 3, no. 9, pp. 1026–1031, 2008.

[39] F. Cappuzzo, T. Ciuleanu, L. Stelmakh, et al., “SATURN: a double-blind, randomized, phase III study of maintenance erlotinib versus placebo following nonprogression with first-line platinum-based chemotherapy in patients with advanced NSCLC,” *Journal of Clinical Oncology*, vol. 27, supplement 15, 2009, abstract no. 8001.

[40] 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 chemotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC),” *Journal of Clinical Oncology*, vol. 27, supplement 18, 2009, abstract no. LBA 8002.

[41] C. Gridelli, C. Butts, F. Ciardiello, R. Feld, C. Gallo, and F. Perrone, “An international, multicenter, randomized phase III study of first-line erlotinib followed by second-line cisplatin/gemcitabine versus first-line cisplatin/gemcitabine followed by second-line erlotinib in advanced non-small-cell lung cancer: treatment rationale and protocol dynamics of the TORCH trial,” *Clinical Lung Cancer*, vol. 9, no. 4, pp. 235–238, 2008.

[42] N. Hanna, F. A. Shepherd, F. V. Fossella, et al., “Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy,” *Journal of Clinical Oncology*, vol. 22, no. 9, pp. 1589–1597, 2004.

[43] F. A. Shepherd, J. R. Pereira, T. Ciuleanu, et al., “Erlotinib in previously treated non-small-cell lung cancer,” *The New England Journal of Medicine*, vol. 353, no. 2, pp. 123–132, 2005.

[44] A. Bezjak, D. Tu, L. Seymour, et al., “Symptomatic 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,” *Journal of Clinical Oncology*, vol. 26, no. 14, pp. 2350–2357, 2008.

[45] D. M. Jackman, B. Y. Yeap, N. I. Lindeman, et al., “Phase II clinical trial of chemotherapy-naive patients ≥ 70 years of age treated with erlotinib for advanced non-small-cell lung cancer,” *Journal of Clinical Oncology*, vol. 25, no. 7, pp. 760–766, 2007.

[46] J. S. Langer, S. Li, J. Schiller, W. Tester, B. L. Raipoort, and D. H. Johnson, “Randomized phase III trial of paclitaxel plus carboplatin or gemcitabine plus cisplatin in eastern cooperative oncology group performance status 2 non-small-cell lung cancer patients: ECOG 1599,” *Journal of Clinical Oncology*, vol. 25, no. 4, pp. 418–423, 2007.

[47] P. J. Hesketh, K. Chansky, D. H. M. Lau, et al., “Sequential vinorelbine and docetaxel in advanced non-small-cell lung cancer patients age 70 and older and/or with a performance status of 2: a phase II trial of the Southwest Oncology Group (S0027),” *Journal of Thoracic Oncology*, vol. 1, no. 6, pp. 537–544, 2006.

[48] C. J. Sweeney, J. Zhu, A. B. Sandler, et al., “Outcome of patients with a performance status of 2 in eastern cooperative oncology group study E1594: a phase III trial in patients with metastatic nonsmall cell lung carcinoma,” *Cancer*, vol. 92, no. 10, pp. 2639–2647, 2001.

[49] R. Lilenbaum, R. Axelrod, S. Thomas, et al., “Randomized phase II trial of erlotinib or standard chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2,” *Journal of Clinical Oncology*, vol. 26, no. 6, pp. 863–869, 2008.

[50] P. J. Hesketh, K. Chansky, A. J. Wozniak, et al., “Southwest Oncology Group phase II trial (S0341) of erlotinib (OSI-774)
Explores EGFR, KRAS mutations and other molecular markers in tumors of NSCLC patients (pts) treated with chemotherapy ± erlotinib (TALENT), in *Proceedings of the Annual Meeting of the American Society of Clinical Oncology*, Orlando, Fla, USA, May 2005, abstract no. 7028.

M. Cobor, F. Cardenal, A. Insa, et al., “Skin rash as surrogate marker of efficacy in patients with non-small cell lung cancer treated with erlotinib,” in *Proceedings of the Annual Meeting of the American Society of Clinical Oncology*, Chicago, Ill, USA, June 2007, abstract no. 7602.

B. E. Johnson and P. A. Janne, “Epidermal growth factor receptor mutations in patients with non-small cell lung cancer,” *Cancer Research*, vol. 65, no. 17, pp. 7525–7529, 2005.

G. Giaccone, “Epidermal growth factor receptor inhibitors in the treatment of non-small-cell lung cancer,” *Journal of Clinical Oncology*, vol. 23, no. 14, pp. 3235–3242, 2005.

H. Shigematsu, L. Lin, T. Takahashi, et al., “Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers,” *Journal of the National Cancer Institute*, vol. 97, no. 5, pp. 339–346, 2005.

G. J. Riely, W. Pao, D. Pham, et al., “Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib,” *Clinical Cancer Research*, vol. 12, no. 3, pp. 839–844, 2006.

D. M. Jackman, B. Y. Yeap, L. V. Sequist, et al., “Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib,” *Clinical Cancer Research*, vol. 12, no. 13, pp. 3908–3914, 2006.

F. R. Hirsch, W. A. Franklin, J. McCoy, et al., “Predicting clinical benefit from EGFR TKIs: not all EGFR mutations are equal,” in *Proceedings of the Annual Meeting of the American Society of Clinical Oncology*, Atlanta, Ga, USA, June 2006, abstract no. 7072.

L. R. Bailey, M. Kris, M. Wolf, et al., “Tumor EGFR membrane staining is not clinically relevant for predicting response in patients receiving gefitinib (Iressa, ZD1839) monotherapy for pretreated advanced non-small cell lung cancer: IDEAL 1 and 2,” *Proceedings of the American Association for Cancer Research*, vol. 44, p. 1362, 2003, abstract no. LB-170.

V. A. Miller, M. Zakowski, G. J. Riely, et al., “EGFR mutation and copy number, EGFR protein expression and KRAS mutation as predictors of outcome with erlotinib in bronchioloalveolar cell carcinoma: results of a prospective phase II trial,” in *Proceedings of the Annual Meeting of the American Society of Clinical Oncology*, Atlanta, Ga, USA, June 2006, abstract no. 7003.

V. M. Villaflor, L. Buckingham, M. Gale, et al., “EGFR mutations (muts), IHC and FISH status, and chromosome 7 gene copy number combined with pAkt expression as potential predictors of survival in non-small cell lung cancer (NSCLC) patients (pts) treated with gefitinib (GEF),” in *Proceedings of the Annual Meeting of the American Society of Clinical Oncology*, Atlanta, Ga, USA, June 2006, abstract no. 7182.

H. S. Parra, R. Cavina, F. Latteri, et al., “Analysis of epidermal growth factor receptor expression as a predictive factor for response to gefitinib (Iressa, ZD1839) in non-small-cell lung cancer,” *British Journal of Cancer*, vol. 91, no. 2, pp. 208–212, 2004.

S.-W. Han, P. G. Hwang, D. H. Chung, et al., “Epidermal growth factor receptor (EGFR) downstream molecules as response predictive markers for gefitinib (Iressa, ZD1839) in chemotherapy-resistant non-small cell lung cancer,” *International Journal of Cancer*, vol. 113, no. 1, pp. 109–115, 2005.

F. Cappuzzo, F. R. Hirsch, E. Rossi, et al., “Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer,” *Journal of the National Cancer Institute*, vol. 97, no. 9, pp. 643–655, 2005.

M. S. Tsao, A. Sakurada, J. C. Cutz, et al., “Erlotinib in lung cancer–molecular and clinical predictors of outcome,” *The New England Journal of Medicine*, vol. 353, pp. 133–144, 2005.

F. R. Hirsch, M. Varella-Garcia, P. A. Bunn Jr., et al., “Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer,” *Journal of Clinical Oncology*, vol. 24, no. 31, pp. 5034–5042, 2006.

T. Takano, Y. Ohe, H. Sakamoto, et al., “Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer,” *Journal of Clinical Oncology*, vol. 23, no. 28, pp. 6829–6837, 2005.

S. A. Ahrendt, P. A. Decker, E. A. Alawi, et al., “Cigarette smoking is strongly associated with mutation of the K-ras gene in patients with primary adenocarcinoma of the lung,” *Cancer*, vol. 92, no. 6, pp. 1525–1530, 2001.

S. Rodenhuis, R. J. C. Slebos, A. J. M. Boot, et al., “Incidence and possible clinical significance of K-ras oncogene activation in adenocarcinoma of the human lung,” *Cancer Research*, vol. 48, no. 20, pp. 5738–5741, 1988.

Y. Suzuki, M. Orita, M. Shiraishi, K. Hayashi, and T. Sekiya, “Detection of ras gene mutations in human lung cancers by single-strand conformation polymorphism analysis of polymerase chain reaction products,” *Oncogene*, vol. 5, no. 7, pp. 1037–1043, 1990.

M. Tsao, C. Zhu, A. Sakurada, et al., “An analysis of the prognostic and predictive importance of K-ras mutation status in the National Cancer Institute of Canada Clinical Trials Group BR.21 study of erlotinib versus placebo in the treatment of non-small cell lung cancer,” in *Proceedings of the Annual Meeting of the American Society of Clinical Oncology*, Atlanta, Ga, USA, June 2006, abstract no. 7005.

C. Gridelli, P. Maione, and A. Rossi, “Chemotherapy and targeted therapy for older patients with advanced non-small cell lung cancer,” in *Educational Book*, pp. 283–287, ASCO, 2009.

C. Gridelli, “Treatment of advanced non-small-cell lung cancer in the elderly: from best supportive care to the combination of platin-based chemotherapy and targeted therapies,” *Journal of Clinical Oncology*, vol. 26, no. 1, pp. 13–15, 2008.

L. P. Fried, C. M. Tangen, J. Walston, et al., “Frailty in older adults: evidence for a phenotype,” *Journals of Gerontology: Series A*, vol. 56, no. 3, pp. M146–M156, 2001.

C. J. Langer, “The Lazarus response” in treatment-Naive, poor performance status patients with non-small-cell lung cancer and epidermal growth factor receptor mutation,” *Journal of Clinical Oncology*, vol. 27, pp. 1350–1354, 2009.

D. Cella, R. S. Herbst, T. J. Lynch, et al., “Clinically meaningful improvement in symptoms and quality of life for patients with non-small-cell lung cancer receiving gefitinib in a randomized controlled trial,” *Journal of Clinical Oncology*, vol. 23, no. 13, pp. 2946–2954, 2005.

A. Inoue, K. Kobayashi, K. Usui, et al., “First-line gefitinib for patients with advanced non-small-cell lung cancer harboring...
epidermal growth factor receptor mutations without indication for chemotherapy,” *Journal of Clinical Oncology*, vol. 27, no. 9, pp. 1394–1400, 2009.

[77] C. Gridelli, P. Maione, D. Galetta, and A. Rossi, “Safety profile of erlotinib in patients with advanced non-small cell lung cancer with chronic renal failure,” *Journal of Thoracic Oncology*, vol. 2, no. 1, pp. 96–98, 2007.

[78] C. Gridelli, A. Rossi, F. Mongillo, M. Baeschino, P. Maione, and F. Ciardiello, “A randomized phase II study of sorafenib/gemcitabine or sorafenib/erlotinib for advanced non-small-cell lung cancer in elderly patients or patients with a performance status of 2: treatment rationale and protocol dynamics,” *Clinical Lung Cancer*, vol. 8, no. 6, pp. 396–398, 2007.