Erlotinib as Second-Line Therapy for Patients with Advanced Non-Small-Cell Lung Cancer and Wild-Type EGFR Tumors

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Abstract: *Aim*: The objective of the study was to determine the efficacy and safety of erlotinib in second-line therapy for patients with advanced non-small-cell lung carcinoma (NSCLC) and wild-type tumors, measuring progression-free survival (PFS), the response rate, and overall survival (OS).

Material and Methods: This retrospective, observational, and multicenter study involved 47 patients diagnosed with NSCLC and wild-type epidermal growth factor receptor (EGFR) who received erlotinib as second-line therapy in four Spanish hospitals. Primary and secondary endpoints included the determination of the efficacy (by measuring progression-free survival, PFS, the response rate, and overall survival, OS) and safety profile of erlotinib.

Results: The median PFS was 2.33 months (95% CI, 0.4–10.9). No differences in PFS were found regarding sex, age, smoking habits, ECOG performance status, and tumor histology. The median OS was 4.00 months (95% CI, 1.18–6.82). Four patients developed grade 3–4 non-hematological toxicities, including asthenia, cutaneous toxicity, and renal failure. One patient developed grade 3–4 thrombocytopenia.

Conclusion: Our study corroborates the modest but clear benefit of second-line agents, including erlotinib, for the treatment of advanced NSCLC, and supports their administration in patients with wild-type EGFR. Further prospective studies involving large number of patients are required to corroborate such results.

Keywords: Non-small-cell lung carcinoma, EGFR, wild-type, erlotinib, second-line.

INTRODUCTION

Non-small-cell lung carcinoma (NSCLC) is one of the leading causes of cancer-related mortality worldwide, with a five-year survival rate lower than 15% because of the advanced and unresectable stage of the disease when diagnosed [1,2]. Platinum-based regimens, considered standard first-line chemotherapy for unselected patients, have demonstrated a modest but significant improvement in survival, compared with supportive care alone [3]. However, chemotherapy treatment for advanced NSCLC often results ineffective and excessively toxic, as the disease normally progresses in most patients within 3–6 months of starting the treatment [4,5]. The median overall survival in the second-line or later setting is established in about 6 months [6]. Therefore providing efficient second- and third-line agents for the palliation of symptoms, improvement of the quality of life (QoL), and prolongation of the overall survival (OS) have become crucial at this time. Current second-line agents for the management of the advanced NSCLC in unselected patients include docetaxel, pemetrexed, or erlotinib [7]. The efficacy of pemetrexed and docetaxel in this setting has been shown to be similar, prolonging progression-free survival (PFS) and OS [8,9]. Erlotinib is the only tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR) that has been proven to extend OS in patients with advanced NSCLC after failure of cytotoxic chemotherapy, as demonstrated in the phase III BR.21 study and corroborated in the phase IV TRUST study [10,11]. Although erlotinib is especially effective in tumors harboring activating mutations in the tyrosine kinase domain of the EGFR gene, some studies have indicated that it is also effective in wild-type EGFR patients [12,13] . The Okayama Lung Cancer Study Group carried out a phase II trial using erlotinib monotherapy in 30 pre-treated patients with advanced NSCLC and no EGFR mutation. Results from this trial showed a modest activity of erlotinib; with 2.1 months of PFS and 9.2 months of OS, and causing no irreversible toxicity [14]. Recently, TAILOR (Tarceva Italian Lung Optimization trial) study compared the efficacy of erlotinib and docetaxel on this group of patients [15]. The oral administration of erlotinib achieved a median PFS and OS of 2.4 and 5.4 months, respectively.

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Despite exploratory trials, studies specifically focused on erlotinib as second-line agent in wild-type EGFR patients are very limited so far. Therefore, the objective of the present study was to provide further information regarding the efficacy and safety of erlotinib in second-line therapy for patients with advanced NSCLC and wild-type tumors in routine clinical practice.

MATERIAL AND METHODS

This retrospective, observational, and multicenter study involved 47 patients diagnosed with NSCLC and wild-type EGFR who received erlotinib as second second-line therapy in 3 Spanish hospitals (Hospital Universitario Lucus Augusti, Complexo Hospitalario Universitario of Vigo and Complexo Hospitalario Universitario of Ourense). The inclusion criteria for participating in the study were as follows: over 18 years old; diagnosis of non-squamous NSCLC in stage IIIB with malignant pleural effusion or stage IV; wild-type EGFR; having received erlotinib orally, 150 mg/day, as second second-line therapy for the advanced disease; Eastern Cooperative Oncology Group performance status, ECOG PS, between 0 and 2. Main exclusion criteria included: having not determined the EGFR status; suffering from a concomitant severe systemic disease, active infection, or neoplasia; having a clinically active interstitial lung disease, or being unable to take the oral drug. All patients gave their informed consent to participate in the study. Procedures were performed in accordance with guidelines established by the Ethics Committee of each participating center, and the Declaration of Helsinki.

Assessment of Efficacy and Safety

The primary endpoint was to determine the efficacy of the treatment by measuring PFS, the response rate, and OS. Survival functions were estimated using Kaplan-Meier method (95% confidence interval, 95% CI). PFS was defined as the elapsed time between the starting erlotinib treatment and disease progression or death, by any cause. PFS was also estimated by taken into account certain characteristics of patients, such as sex, age (≤62 versus >62 years old), smoking habits, ECOG PS, and tumor histology (adenocarcinoma versus others). Log-rank test was performed to compare PFS between groups. A univariate Cox regression analysis was performed to identify prognostic factors associated with PFS. Independent variables with significance p≤0.1 were introduced in the multivariate analysis. OS was defined as the time between the starting erlotinib treatment and death, by any cause. Complete Response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were evaluated by following RECIST criteria [16]. Secondary endpoint included the evaluation of the safety profile. Quantitative values were expressed as median and the range, including minimum and maximum values. The statistical significance was established for p≤0.05. All statistical procedures were performed by using SPSS 17.0 software (IBM, Chicago, Illinois, USA).

Table 1: Characteristics of Patients and Tumors at Baseline

	Total (n=47)
Sex male, n (%)	39 (83.0)
Age, median age (range)	62.0 (38.0–83.0)
Smoking habits, n (%)	
Smokers	16 (37.2)
Ex-smokers	18 (41.9)
Non-smokers	9 (20.9)
ECOG PS, n (%)	
0	4 (8.5)
1	36 (76.6)
2	7 (14.9)
Tumor histology, n (%)	
Adenocarcinoma	38 (80.9)
Large-cell lung carcinoma	2 (4.3)
Others	7 (14.9)
Staging of lung cancer, n (%)	
Primary tumor	
T1b	2 (4.3)
T2 / T2a	11 (23.4) / 1 (2.1)
T3	4 (8.5)
T4	21 (44.7)
Tx	8 (17.0)
Regional lymph nodes	
N0	9 (19.1)
N2	18 (38.3)
N3	17 (36.2)
Nx	3 (6.4)
Distant metastasis	
M0	1 (2.1)
M1/ M1a	43 (91.5) / 3 (6.4)
Main metastasis locations, n (%)	
Bone	18 (38.3)
Lungs	15 (31.9)
Kidney	13 (27.7)
Pleura	13 (27.7)

ECOG PS; Eastern Cooperative Oncology Group performance status.

RESULTS

From the total of 47 patients, 39 (83.0%) were men and 8 (17.0%) women, with a median age of 62.0 years (range, 38.0–83.0). Characteristics of patients and tumors at baseline are shown in Table **1**.

At baseline, 37.2% were smokers, 41.9% ex-smokers, and 20.9% non-smokers. ECOG PS 1 was found in 76% of patients. The most common type of tumor was adenocarcinoma, in 80.9% of patients. According to the 7th Edition of TNM in lung cancer [17], most of patients had T4 primary tumor (44.7% of patients), followed by T2 (25.5%), N2 regional lymph nodes in (38.3%), followed by N3 (36.2%), and M1 distant metastasis (97.9%). Most frequent locations of metastasis were bone (38.3% of patients), lungs (31.9%), kidney (27.7%), and pleura (27.7%). All patients had previously received first-line therapy for NSCLC. Characteristics of first-and second-line therapies are shown in Table **2**.

Table 2: Characteristics of First-and Second-Line Therapies

	Total (n=47)
First-line therapies, n (%)	
Platinum-based doublets (+ pemetrexed)	23 (48.9)
Cisplatin + pemetrexed	20 (42.6)
Carboplatin + pemetrexed	3 (6.4)
Platinum-based triplets (+ bevacizumab)	12 (27.7)
Carboplatin + docetaxel + bevacizumab	12 (25.5)
Carboplatin + vinorelbine + bevacizumab	1 (2.1)
Platinum-based doublets	6 (12.8)
Cisplatin + docetaxel	5 (10.6)
Carboplatin + docetaxel	1 (2.1)
Others	5 (10.6)
Pemetrexed	3 (6.4)
Vinorelbine	2 (4.3)
Second-line erlotinib therapy, (%)	
Time from diagnosis, median months (range)	7.1 (2.3–69.3)
Time from end of first-line therapy, median months (range)	0.9 (0.0–16.1)
Duration of therapy, median months (range)	2.6 (0.4–11.2)

The most common regimens consisted in platinum-based doublets, including pemetrexed (48.9% of patients), followed by platinum-based triplets, including bevacizumab (27.7%). The median time from diagnosis was 7.1 months (range, 2.3–69.3). The duration of erlotinib treatment as a second-line therapy was 2.6 months (range, 0.4–11.2).

Efficacy Results

Whereas none of the patients achieved a CR, PR was observed in only one (2.1% of patients). Best responses to erlotinib treatment are summarized in Table **3**.

Table 3: Best Responses to Second-Line Erlotinib Treatment

	Total (n=47)
Tumor responses, n (%)	
CR	0 (0.0)
PR	1 (2.1)
SD	7 (14.9)
PD	31 (66.0)
Unknown	8 (17.0)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The SD was found in 14.9% of patients. The median time to achieve the best response to the treatment was 2.3 months (range, 0.4–7.0). The median PFS was 2.33 months (95% CI, 0.4–10.9, Figure **1**).

The estimated proportion of patients with no disease progression or exitus was 38.3% (95% CI, 24.4–52.2) at 3 months, 6.4% (95% CI, -0.6–13.4) at 6 months, and 2.1% (95% CI, -2.0–6.2) at 9 months. Regarding sex, median PFS was longer in females (2.67 months; 95% CI, 1.33–4.01) than males (2.33 months; 95% CI, 1.80–2.86); however these differences were not statistically significant. PFS was not different between patients aged ≤62 years old (2.33 months; 95% CI, 1.73–2.93) and >62 years (2.33 months; 95% CI, 1.07–3.60). Although no statistically significant, non-smokers (3.33 months; 95% CI, 3.04–3.63) showed longer PFS than smokers (2.33 months; 95% CI, 2.14–2.53) and ex-smokers (2.13 months; 95% CI, 1.93–2.34). Regarding PS, PFS was slightly longer in patients with ECOG 0 (2.67 months; 95% CI, 2.31–3.03), and ECOG 1 (2.33 months; 95% CI, 1.65–3.02) than with ECOG 2 (1.40 months; 95% CI, 0.89–1.91); however these differences were not significant. No differences in PFS were found between patients with adenocarcinoma (2.33 months; 95% CI, 1.68–

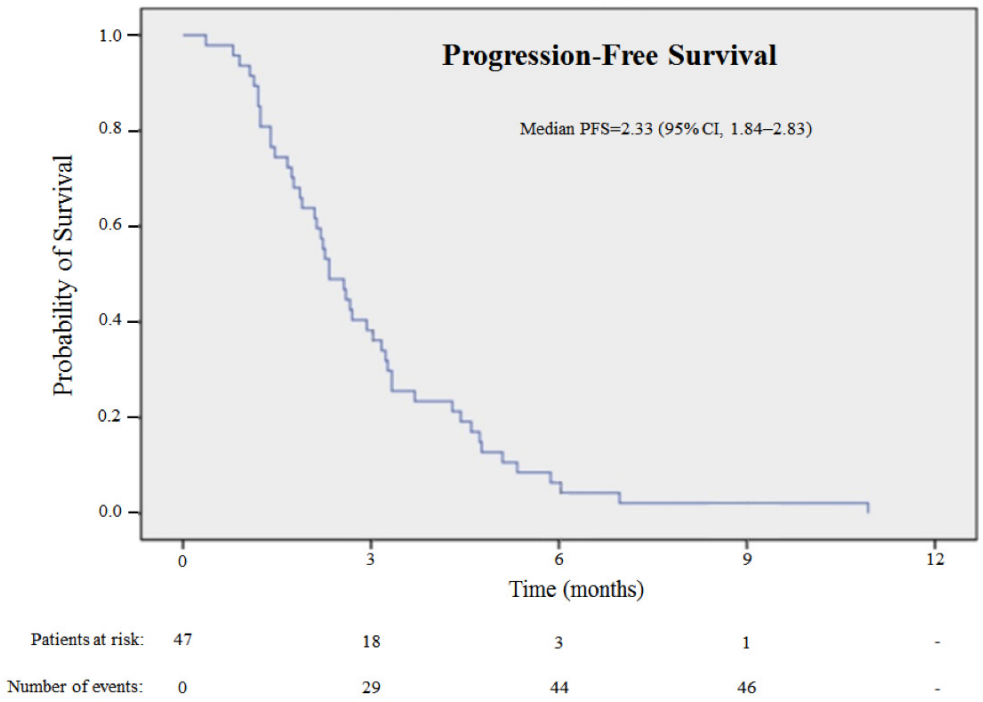

Figure 1: Kaplan-Meier estimates of progression-free survival for erlotinib as second-line therapy in patients with wild-type EGFR tumors.

2.99) and other histological tumors (2.33 months; 95% CI, 0.97–3.70). Only age and PS, as independent factors, were introduced in the multivariate analysis (p≤0.1); however none of them showed a significant association with PFS (data non-shown). The median OS was 4.00 months (95% CI, 1.18–6.82, Figure **2**).

The estimated survival was 59.6% (95% CI, 45.6–73.6) at 3 months, 44.7% (95% CI, 30.5–58.9) at 6 months, 21.7% (95% CI, 9.5–33.9) at 12 months, 10.9% (95% CI, 1.2–20.6) at 18 months, 5.4% (95% CI, -1.8–12.6) at 24 months, 5.4% (95% CI, -1.8–12.6) at 42 months.

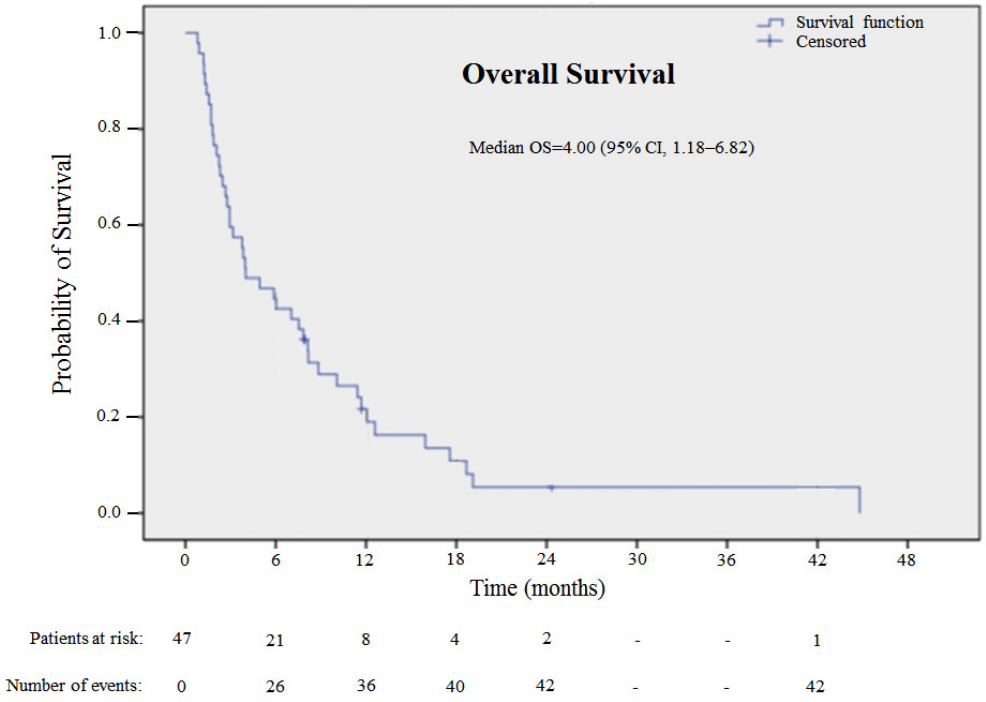

Figure 2: Kaplan-Meier estimates of overall survival for erlotinib as second-line therapy in patients with wild-type EGFR tumors.

Safety Profile

A total of 33 patients (70.2%) developed grade 1–2 non-hematological toxicities, mainly consisting in cutaneous toxicity (in 29.8% of patients), diarrhea (25.5%), and asthenia (21.3%). The safety profile of erlotinib as second-line therapy is shown in Table **4**.

Table 4: Safety Profile of Erlotinib as Second-Line Therapy in Wild-Type EGFR Patients

	Total (n=47)
Main non-hematological adverse events, n (%)	
Grade 1–2	33 (70.2)
Cutaneous toxicity	14 (29.8)
Diarrhea	12 (25.5)
Asthenia	10 (21.3)
Grade 3–4	4 (8.5)
Asthenia	2 (4.3)
Cutaneous toxicity	1 (2.1)
Renal failure	1 (2.1)
Main hematological adverse events, n (%)	
Grade 1–2 anemia	5 (10.6)
Grade 3–4 thrombocytopenia	1 (2.1)
Patients requiring treatment interruption, n (%)	4 (8.5)
Patients requiring dose reduction, n (%)	4 (8.5)
Reasons for discontinuation of the drug, n (%)	
Disease progression	35 (74.5)
General health deterioration	4 (8.5)
Toxicity	3 (6.4)
Exitus	3 (6.4)
Acute renal failure	1 (2.1)
Not specified	1 (2.1)

Only 4 patients (8.5%) developed grade 3–4 non-hematological toxicities, including asthenia (4.3% of patients), cutaneous toxicity (2.1%), and renal failure (2.1%). Regarding hematological toxicities, 5 patients (10.6%) experienced grade 1–2 anemia, and 1 patient (2.1%) developed grade 3–4 thrombocytopenia. From all patients, only 4 (8.5%) required the interruption of the treatment for a median duration of 14.0 months (range, 7.0–20.0). Similarly, 4 patients (8.5%) required dose reduction during the treatment. Disease progression was the main reason for discontinuation of the drug (in 74.5% of patients), followed by general health deterioration (8.5%). From patients, 8 (17.0%) needed hospitalization during the follow-up. Finally, after erlotinib treatment, 17 patients (36.2%) required a third-line therapy, mainly consisting in docetaxel (12.8% of patients) or pemetrexed (8.5%).

DISCUSSION

Main aims of second-line therapies for advanced NSCLC include the palliation of symptoms, improvement of the QoL, and the prolongation of the OS as long as possible. Current strategies in this setting include the administration of docetaxel, pemetrexed, or erlotinib [18–20]. There are several main randomized trials involving erlotinib in patients with advanced NSCLC. The pivotal phase III BR.21 initially evaluated the QoL of 731 patients with NSCLC receiving erlotinib or placebo after disease progression with at least one prior chemotherapy regimen [10]. Erlotinib treatment achieved a PFS and OS of 2.2 and 6.7 months, respectively. One-year survival rate was 31.2% for the erlotinib arm. Although BR.21 study did not consider the EGFR status of tumors, a subsequent exploratory analysis identified 115 wild-type EGFR patients receiving erlotinib [21]. In these patients, the median survival achieved with erlotinib was 7.9 months, *versus* 3.3 months with placebo. The survival benefit between erlotinib and placebo arms was slightly greater, but not statistically significant, for patients with EGFR mutations than with EGFR wild-type or indeterminate variants. Results from BR.21 were afterwards corroborated in the phase IV TRUST (Tarceva Lung Cancer Survival Treatment) trial, designed for up to 6,580 patients with stage IIIB and IV NSCLC who had previously failed for chemotherapy or radiotherapy regimens [11]. In these patients, PFS and OS were 3.25 and 7.9 months, respectively. The one-year survival rate was established in 37.7%. Since the analysis of EGFR mutations was only available in 4.4% of patients, the correlation between survival rates and EGFR was not possible. Taking into account the patients receiving erlotinib only as second-line therapy, PFS and OS was 3.2 and 8.6 months, respectively [22]. The phase III trial, TITAN (Tarceva In Treatment of Advanced NSCLC), compared the efficacy and safety of erlotinib and standard chemotherapy regimens (docetaxel or pemetrexed) among 424 patients with locally advanced, recurrent, or metastatic NSCLC who had received up to four cycles of first-line platinum doublet chemotherapy regimens [23]. Among wild-type EGFR patients, the effect of erlotinib in OS was slightly higher (6.6 months) than traditional chemotherapy (4.4

months). This result corroborated the hypothesis consisting in that the benefit provided by erlotinib is not only due to the presence of activating mutations in EGFR, thus supporting its administration in second and later-lines of therapies regardless tumor EGFR status. The placebo-controlled phase III SATURN (Sequential Tarceva in Unresectable NSCLC) trial evaluated erlotinib as maintenance treatment for advanced NSCLC [24,25]. A total of 437 patients receiving erlotinib achieved a PFS of 12.3 weeks, and OS of 12.0 months. PFS and OS were significant prolonged by erlotinib, versus placebo, in both wild-type and mutant EGFR groups. According to the response to first-line chemotherapy, wild-type EGFR patients with SD receiving erlotinib achieved a benefit in PFS (12.1 weeks) and OS (12.4 months), compared with placebo (11.3 weeks and 8.7 months, respectively) [26]. Finally, the recent phase III HORG (Hellenic Oncology Research Group) study, comparing the efficacy and safety of pemetrexed versus erlotinib in 357 pre-treated patients with advanced NSCLC, [27]. However, the time to progression was significantly higher in patients with squamous cell histology who received erlotinib (4.1 months) compared with pemetrexed (2.5 months).

Despite these exploratory trials, studies specifically focused on erlotinib as second-line agent in wild-type EGFR patients are very limited so far [18]. Results from Okayama Lung Cancer Study Group showed a modest activity of erlotinib on these Japanese patients; with 2.1 months of PFS and 9.2 months of OS, and causing no irreversible toxicity [14]. In addition, the administration of erlotinib in the phase III TAILOR trial, performed to be compared with docetaxel as second-line therapy in wild-type EGFR, achieved a PFS and OS of 2.4 and 5.4, respectively; versus 2.9 and 8.2 months, respectively, with docetaxel [15]. Regarding toxicity, main grade 3–4 effects included dermatological toxicities (rash, nail disorders, dry skin, and pruritus) for erlotinib, and neutropenia, alopecia and neurological, for docetaxel. TAILOR concluded that docetaxel was more effective than erlotinib in this setting; however since this trial presented several methodological inconsistences, mainly due to the change of experimental design and endpoints after its initiation or the unbalanced distribution of patient's characteristics among the experimental groups, conclusions should be cautiously considered. Furthermore, survival results and best response to treatment (5.2% of patients with CR) achieved with docetaxel were slightly higher than previously demonstrated in pivotal and other phase III studies [8,28]. Likewise, the incidence of some side effects, such as neutropenia, was lower than expected. Results from our study are in concordance with literature, and corroborate the activity of erlotinib in second-line setting; achieving 2.33 months of PFS and 4.00 months of OS. Regarding safety, asthenia, cutaneous toxicity, renal failure, and thrombocytopenia were the most common grade 3–4 toxicities.

Some demographic and clinical characteristics of patients, such as female sex, East Asian ethnicity, PS, never-smoker, and adenocarcinoma histology, have been associated with activating mutations in the EGFR and thus with higher sensitivity to erlotinib and better tumor response rates [12,29]. From them, never-smoking women with non-squamous histology and PS 0 have been demonstrated to achieve a significant benefit with erlotinib treatment [30]. Taken into account that all patients from our study were wild-type EGFR, no relevant factor resulted significantly associated with PFS. Nevertheless, our patients were mainly men (83.0%) and smokers (37.2%), two characteristics associated with worse outcomes. Erlotinib impacts positively on the QoL of patients by being orally administered [18]. Moreover, it may be recommended on patients who cannot receive chemotherapy as second-line treatment. Likewise, because the low rate of incidence for febrile neutropenia (FN), erlotinib may be adequate for patients with history of FN or myelosuppression. The main limitations of the study were the retrospective nature of the available data, the low number of patients, and the lack of a control group for comparison. However, in our opinion, our study provides further information about efficacy and safety of erlotinib in clinical practice for unselected patients with NSCLC (stage IIIB and malignant pleural effusion or stage IV) and wild-type EGFR tumors, supporting its use in this setting of the therapy.

In conclusion, our study corroborates the modest but clear benefit of second-line agents, including erlotinib, for the treatment of advanced NSCLC, and supports their administration in patients with wild-type EGFR tumors. Further prospective studies involving large number of patients are required to corroborate such results.

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