

# Early radiological response as predictor of overall survival in non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor mutations

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**Background:** Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) are the standard treatment of advanced, *EGFR*-mutant non-small-cell lung cancer (NSCLC). Usually, radiographic assessment of response to chemotherapy is performed after the patient completes the second course of treatment. The optimal timing of response evaluation for patients receiving EGFR-TKIs is, however, not well-defined. The purpose of this study is to evaluate the association of an early radiological response (ERR) to TKIs by computed tomography (CT) with progression-free survival (PFS) and overall survival (OS) in advanced NSCLC patients with *EGFR* mutations.

**Methods:** *EGFR* mutation status was analyzed retrospectively in a cohort of 360 NSCLC patients' between January 2009 and November 2014. Forty of them received treatment with TKI and therefore were included in the study. Response to TKI therapy was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. ERR was defined as complete response (CR) or partial response (PR) at the first radiographic evaluation performed within 6–8 weeks after the beginning of the treatment.

**Results:** Activating mutations in the tyrosine kinase domain of the *EGFR* gene were mainly exon 19 deletions. Thirty patients (75%) had ERR, 4 of those patients (10%) showed a PR on early CT achieving a CR in the long-term monitoring. Median PFS was longer in patients experiencing an ERR (10.9 *vs.* 2.4 months; HR: 0.42; 95% CI: 0.19–0.93; P=0.033) than those that did not [stable disease (SD) or progressive disease (PD)]. Median overall survival OS was also significantly increased in patients experiencing ERR (23.2 *vs.* 11.9 months; HR: 0.3; 95% CI: 0.15–0.85; P=0.021).

**Conclusions:** ERR in patients treated with EGFR TKI therapy is associated with statistically significant PFS and OS, and could be a surrogate marker of efficacy in these patients. Moreover, ERR provides an early identification of patients not benefitting from TKI, despite the presence of activating *EGFR* mutations in which further efforts are needed to improve their prognosis.

**Keywords:** Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR) mutations; early radiological response (ERR)

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## Introduction

Lung cancer is the leading cause of cancer-related death in worldwide, with higher mortality rates than any other type of cancer (1). Approximately 85% is non-small cell lung cancer (NSCLC). Most patients present with advanced or metastatic disease, where the surgery is not indicated. Furthermore, a significant proportion of patients diagnosed with early-stage NSCLC eventually experience metastatic disease or regional relapse (1,2).

Platinum-based doublet chemotherapy combinations, which have represented the cornerstone of the initial treatment for most patients with advanced NSCLC, confer a survival benefit which is equivalent to a 9% absolute improvement in 1-year survival rates (increasing survival from 20% to 29%) (3). In the last decade, the identification of molecular subtypes of NSCLC has significantly modified the management and prognosis of a subset of patients. The discovery of epidermal growth factor receptor (*EGFR*) mutations and *ALK/ROS1* translocations (4-9), and the significant progression-free survival (PFS) advantage of *EGFR* (erlotinib, gefitinib, afatinib) or *ALK/ROS1* (crizotinib) inhibitors over chemotherapy in this subpopulation in large randomized trials (6-13) has led to a biomarker-based approach for the selection of first-line therapy. Additionally, anti-PD-1/PD-L1 agents have shown higher efficacy compared with chemotherapy, firstly in second-line setting and lately as first-line therapy in patients with metastatic NSCLC with a  $\geq 50\%$  PD-L1 expression (14-18). Therefore, currently patients with *EGFR* mutations or *ALK/ROS1* translocations are eligible for treatment with *EGFR* or *ALK/ROS1* tyrosine kinase inhibitors (TKIs), respectively, while patients without a known driver mutation generally receive treatment with immunotherapy (if  $\geq 50\%$  PD-L1 expression) or platinum-doublet chemotherapy combinations (if  $< 50\%$  PD-L1 expression) (14,15).

Despite the significant response rates (RRs) observed with *EGFR* TKIs in *EGFR* positive tumors, response to therapy is not uniform (19) and identifying patients that will respond to therapy remains a challenge. In patients receiving cytotoxic agents, objective tumor regression measured as overall response rate (ORR) has been used as primary efficacy endpoint in drug development, and radiologic assessment following Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, is currently recommended after the completion of two or three cycles of chemotherapy (19,20). However, the mechanism of action of molecular targeted agents such as *EGFR* TKIs is different, raising

questions as to whether RECIST version 1.1 can serve as an appropriate efficacy endpoint. Moreover, the optimal timing for response evaluation of *EGFR* TKI is not well-defined, since response can be observed as early as a few days after treatment initiation (16,19,21-24).

We performed a retrospective, single centre study to evaluate the association between early radiological response (ERR) with survival in *EGFR*-mutated NSCLC patients treated with first- or second-generation *EGFR* TKIs.

## Methods

### Study design

Locally advanced (no suitable for radical treatment) or metastatic NSCLC *EGFR* mutated patients diagnosed between January 2009 and November 2014 in the Hospital Universitari i Politècnic La Fe in Valencia (Spain) were included in this study. Eligibility criteria included: (I) histologically confirmed NSCLC with locally advanced or metastatic disease (stage IIIB or IV); (II) presence of activating *EGFR* mutation; (III)  $\geq 18$  years old; (IV) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; and (V) treatment with *EGFR* TKIs gefitinib, erlotinib or afatinib once daily at least for 2 weeks.

Response to *EGFR* TKI therapy was defined according to RECIST version 1.1 (24). ERR was defined as complete response (CR) or partial response (PR) at first radiographic evaluation performed after 6-8 weeks from the beginning of treatment.

Initial patient evaluation included a complete blood count, biochemical evaluation [albumin, renal function, liver enzymes, lactate dehydrogenase (LDH)], an electrocardiogram, a chest X-ray and computed tomography (CT)-scan for evaluation of disease extension.

Clinical data were derived from review of electronic medical records. Variables considered in our study were: sex, age, race, smoking, disease stage, histological type, presence of metastasis and their location, type of treatment, chemotherapy and its characteristics (first and successive treatment lines), treatment with TKI, toxicities, treatment delays due to toxicity, supportive treatment. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria version 4.

### Tissue and *EGFR* analysis

Initial histological diagnosis was performed on formalin-

fixed paraffin-embedded (FFPE) tissue. Five  $\mu\text{m}$  thick sections were macrodissected by a pathologist to select regions containing the highest proportion of tumor cells. Genomic DNA was isolated from FFPE sections using Deparaffinization Solution and QIAamp DNA Investigator Kit (Qiagen, Hilden, Germany) according to manufacturer's protocol. DNA concentration was quantified by spectrophotometer using NanoDrop 2000c (ThermoFisher Scientific, Waltham, MA, USA). Samples were tested by real time polymerase chain reaction (PCR) in a cobas z480 analyzer using the cobas<sup>®</sup> *EGFR* Mutation Test v2 (CE-IVD; Roche Molecular Diagnostics, Basel, Switzerland), which can detect 42 mutations in exons 18–21 of the *EGFR* gene.

### Statistical analysis

A descriptive analysis of patient characteristics, treatments administered and their most relevant toxicities was performed. Treatment response (TR) rates, toxicities, PFS and overall survival (OS) rates were estimated as proportions (%); comparisons between proportions were estimated using the Chi-square test. PFS and OS were estimated by the Kaplan-Meier method and differences among the different groups were analyzed with log-rank test (P values below 0.05 were considered statistically significant).

Univariate Cox hazards regression models were used to evaluate the association of smoking, PS, ERR, line of treatment and type of *EGFR* mutation with OS. Variables with a P value <0.1 in univariate analysis were selected for inclusion in the multivariate model. Additionally, investigators decided to include mutation type in the multivariate model despite it not reaching a significant P value due to its clinical relevance. Multivariate Cox hazards regression analysis was used to evaluate independent prognostic factors associated to OS. ERR, line of treatment and type of *EGFR* mutation were used as covariates. Variables with a P value lower than 0.05 were considered to indicate statistical significance. Statistical analysis and graphical representations were performed using SPSS statistics v19 (IBM, Armonk, NY, USA).

## Results

### Patients' characteristics

Between January 2009 and November 2014, *EGFR* mutation status was analysed in 360 NSCLC patients. Fifty-five patients (55/360; 15.3%) were *EGFR* mutation positive and

40 of them met inclusion criteria (*Figure S1*). The clinical and pathologic characteristics of the 40 eligible patients are summarized in *Table 1*. *EGFR* mutations identified in the tumors, were mainly exon 19 deletions (17/40 patients; 42.5%), and L858R point mutation (16/40 patients; 40.0%). Median follow-up was 21 months (range, 2–75 months). At the moment of the analysis, 25 patients (62.5%) had died.

### TKI response and survival

Thirty patients (75%) experienced an ERR; of these, 4 experienced a CR and 26 had a PR. Of those patients with a PR as their ERR, 4 eventually experienced a CR on subsequent radiographic assessments. Ten patients (25%) did not experience an ERR; of these, 5 experienced stable disease (SD) and 5 experienced progressive disease (PD). None of the patients that did not achieve an ERR experienced any type of response (PR or CR) on subsequent radiographic assessments. Oligoprogression was not observed in any patient.

Median PFS was significantly longer in patients experiencing an ERR (CR or PR) (10.9 *vs.* 2.4 months; HR: 0.42; 95% CI: 0.19–0.93; P=0.033) than those with SD or PD (*Figure 1*). Median OS was also significantly increased in patients experiencing an ERR (23.9 *vs.* 11.9 months; HR: 0.3; 95% CI: 0.15–0.85; P=0.021).

On univariate analysis, ERR and line of treatment were the only variables significantly associated with OS (*Table S1*). Although the type of mutation did not reach a significant P value on univariate analysis, the authors decided to include it in the multivariate analysis due to its clinical relevance. In the multivariate Cox hazards regression model, only ERR remained as an independent variable (HR: 0.36; 95% CI: 0.16–0.86; P=0.021) (*Table S2*).

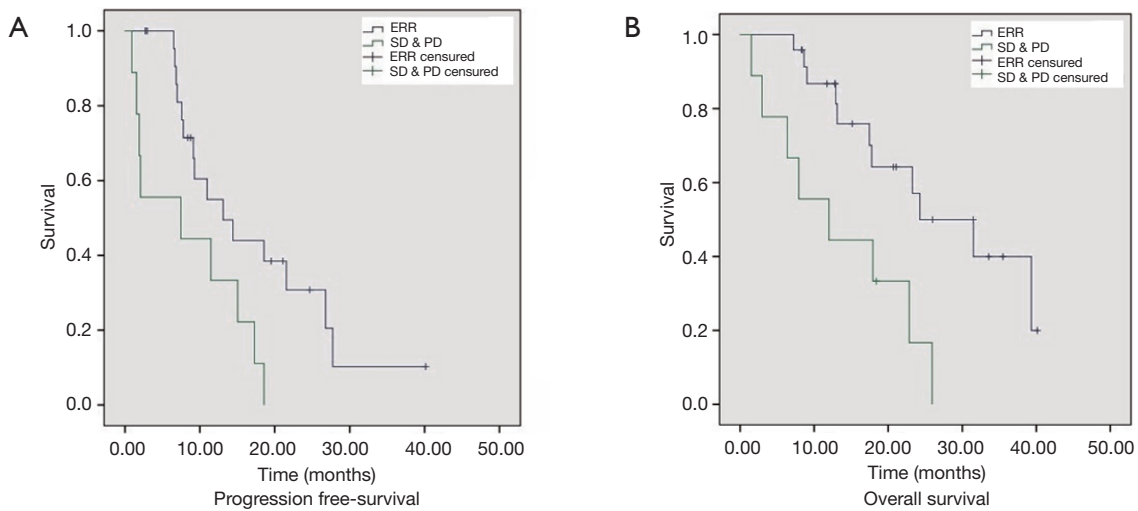
### EGFR mutation subtypes and survival

We also evaluated the relationship between treatment efficacy and the different *EGFR*-mutation subtypes. The ERR rate was 76.5% (13/17) in patients harboring exon 19 deletions and 69% (11/16) in patients bearing L858R point mutations; no significant differences were observed between groups (P=0.619). When considering only those patients with activating *EGFR* mutations (exon 19 deletions or L858R point mutations), a similar survival benefit in those experiencing an ERR was observed. Median PFS (13 *vs.* 7 months; HR: 0.368; 95% CI: 0.154–0.881; P=0.025) and OS (24 *vs.* 12 months; HR: 0.278; 95% CI:

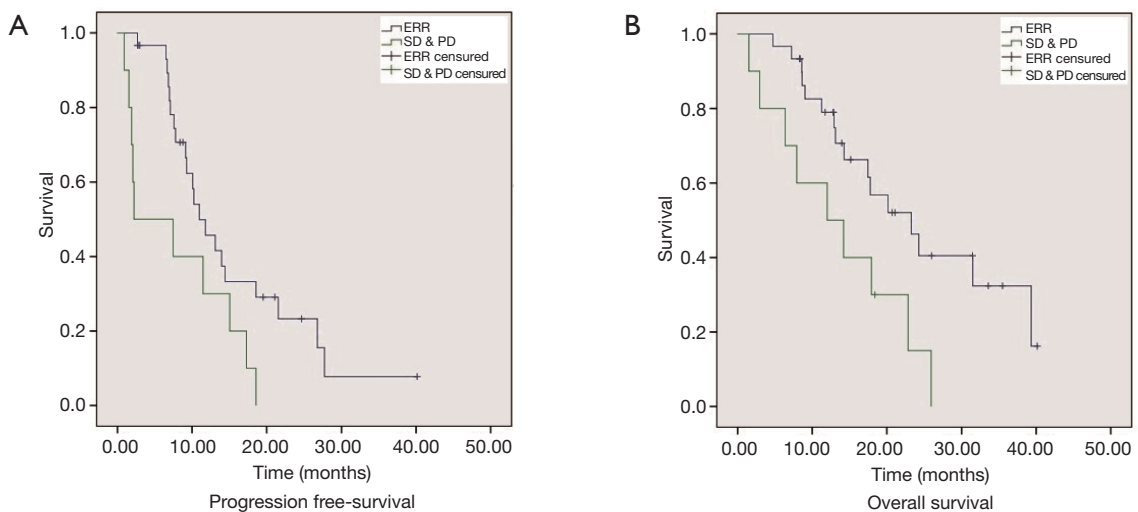
**Table 1** Patients clinic-pathologic characteristics

Variables	All patients	Patients with ERR	Patients without ERR
Patients enrolled, n (%)	40 (100.0)	30 (75.0)	10 (25.0)
Gender, n (%)			
Male	19 (47.5)	14 (46.7)	5 (50.0)
Female	21 (52.5)	16 (53.3)	5 (50.0)
Age, years			
Median [range]	62 [40–85]	61 [40–85]	69 [41–84]
Race, n (%)			
European	38 (95.0)	28 (93.3)	10 (100.0)
Others	2 (5.0)	2 (6.7)	0
Smoking, n (%)			
Yes	9 (22.5)	6 (20.0)	3 (30.0)
No	30 (75.0)	23 (76.7)	7 (70.0)
Unknown	1 (2.5)	1 (3.3)	0
Packs, years			
Median [range]	0 [0–185]	0 [0–185]	0 [0–102]
Performance status, n (%)			
0	14 (35.0)	10 (33.3)	4 (40.0)
1	22 (55.0)	16 (53.3)	6 (60.0)
2	4 (10.0)	4 (10.3)	0
Pathology, n (%)			
Adenocarcinoma	39 (97.5)	29 (96.7)	10 (100.0)
Others	1 (2.5)	1 (3.3)	0
Stage, n (%)			
IIIB	2 (5.0)	2 (6.7)	0
IV	38 (95.0)	28 (93.3)	10 (100.0)
Number of prior CT, n (%)			
0	25 (62.5)	21 (70.0)	4 (40.0)
1	10 (25.0)	7 (23.3)	3 (30.0)
2	3 (7.5)	1 (3.3)	2 (20.0)
>2	2 (5.0)	1 (3.3)	1 (10.0)
TKI, n (%)			
Erlotinib	30 (75.0)	23 (76.7)	7 (70.0)
Gefitinib	8 (20.0)	6 (20.0)	2 (20.0)
Afatinib	2 (5.0)	1 (3.3)	1 (10.0)

ERR, early radiological response; CT, computed tomography; TKI, tyrosine kinase inhibitor.



**Figure 1** Progression-free survival (PFS) (A) and overall survival (OS) (B) of patients with early radiological response (ERR) *vs.* stable disease (SD) and progressive disease (PD).



**Figure 2** Progression-free survival (PFS) (A) and overall survival (OS) (B) of patients with activating-mutations with early radiological response (ERR) *vs.* stable disease (SD) and progressive disease (PD).

0.106–0.731;  $P=0.009$ ) was significantly longer in patients that experienced an ERR than those experiencing SD or PD (Figure 2).

#### *Treatment-related adverse effects*

The most frequent treatment-related adverse effects were grade 1–2 skin toxicity (rash and dryness) in 59% of patients. Treatment was interrupted in 5 patients (13%) because of skin toxicity (rash). Dose reduction was required

in 8 patients (20%) due to skin toxicity ( $n=4$ ; 10%) and worsening of general condition ( $n=4$ ; 10%).

#### **Discussion**

*EGFR* activating mutations represent the first molecular biomarker implemented for clinical use in lung cancer, leading to the use of TKIs as standard first line therapy in a subset of patients. Although radiographic response criteria (RECIST v1.1) evaluated after 2–3 cycles of chemotherapy

is a well-established efficacy end-point for cytotoxic chemotherapy, its validity as an efficacy biomarker in patients treated with TKIs is less well recognized.

The optimal time-point for the initial response evaluation to TKIs remains a matter of debate. Most pivotal trials that comparing TKIs to chemotherapy used the first response evaluation performed after 6–8 weeks of treatment (6,7,21,22) as the efficacy endpoint. However, response to therapy as early as days after treatment initiation has been reported (19). Some studies have tried to correlate responses at earlier time-points with the outcome of TKI therapy in patients with NSCLC and *EGFR* mutations (4-26). Chang *et al.* reported an association between the early radiological image change and the overall radiographic response, although the difference was not statistically significant, possibly due to the reduced number of patients enrolled (19). An association between ERR, measured by positron emission tomography (PET), with RECIST response in patients treated with gefitinib and erlotinib has been reported (23-25); the role of PET in this context must, however, still be determined (23-25). In other clinical scenarios, such as neoadjuvant chemotherapy in patients with locally advanced tumors, an association between radiographic response and survival has also been reported (24,26).

The clinical characteristics of patients participating in our study are similar to those reported in previous studies evaluating *EGFR* mutant NSCLC cohorts, except for a similar proportion of women and men observed in our cohort. Treatment efficacy, despite the fact most patients have received one or more previous treatments, was similar to previously published studies (6-8).

In our group of *EGFR*-mutant NSCLC patients treated with TKIs, ERR was found to be associated with significantly higher median PFS and OS (10.9 *vs.* 2.4 months and 23.9 *vs.* 11.9 months, respectively) than patients who achieved SD or PD at first radiographic evaluation. Our results confirm the association between RR and OS, that has been reported in a systematic review of 28 trials with *EGFR* TKI monotherapy (27), as well as observations previously reported by Chang *et al.* (19), whereby patients with activating *EGFR* mutations experience proportionally higher ORR to *EGFR*-TKI treatment. In our study, the difference in survival observed in the subgroup of patients harboring *EGFR* activating mutations that experienced ERR and those with SD or PR was even larger than in the general population.

Overall, the results of this study suggest that patients

treated with TKI that do not respond at the first evaluation have a worse prognosis, which is independent of the presence of *EGFR* mutations, with PFS and OS values that are similar to those reported for patients treated with chemotherapy (16). Close monitoring of these patients in order to detect an early progression could potentially enable a switch to alternative treatment options before clinical progression occurs.

Limitations of our study include the heterogeneity of the population, with different types and lines of treatments, the small sample size and the retrospective character of the analysis. The presence of *T790M* mutations at progression was not clinically assessed in our centre during the times when most of participants were treated. Moreover, no patients in the study experimented oligoprogression. Therefore, our results cannot be extrapolated to patients experiencing oligoprogression at an early radiographic assessment while on *EGFR* TKIs. All these issues should be considered in future prospective studies.

In conclusion, ERR may serve as an early indicator of TKI inhibitor efficacy in *EGFR* mutant NSCLC patients. Although the early identification of non-responders could allow an early treatment switch while PS is still optimal, which could increase the efficacy of subsequent lines of treatment, continuation of treatment with TKIs is currently recommended in cases of oligoprogressive disease (28). Data from prospective cohorts will be needed to elucidate the value of early responses in patients treated with *EGFR* TKIs, in order to maximize outcome.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study was approved by institutional ethics committee of “Comité Ético de Investigación Biomédica Hospital La Fe” (No. 2015/0345).

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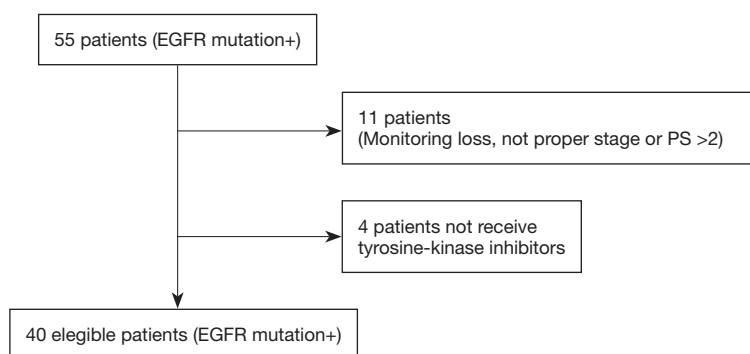


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**Figure S1** Algorithm patient selection. EGFR, epidermal growth factor receptor; PS, performance status.

**Table S1** Univariate analysis

Variable	HR	95% CI	P value
Mutation type	1.10	0.71–1.56	0.788
Line of treatment	1.02	0.99–1.03	0.043
ERR	0,37	0.16–0.87	0.024
Smoking	1.03	0.67–1.57	0.895
Performance status	0.98	0.59–1.93	0.960

ERR, early radiological response; HR, hazard ratio; CI, confidence interval.

**Table S2** Multivariate analysis

Variable	HR	95% CI	P value
ERR	0.36	0.16–0.86	0.021
Mutation type	1.15	0.77–1.72	0.491
Line of treatment	1.02	1.00–1.03	0.033

ERR, early radiological response; HR, hazard ratio; CI, confidence interval.