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Brain metastases from lung cancer responding to erlotinib: the importance of *EGFR* mutation

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ABSTRACT: Median survival of patients with brain metastases from nonsmall cell lung cancer (NSCLC) is poor and more effective treatments are urgently needed. We have evaluated the efficacy of erlotinib in this setting and its association with activating mutations in the epidermal growth factor receptor (*EGFR*) gene.

We retrospectively identified patients with NSCLC and brain metastases treated with erlotinib. *EGFR* mutations in exons 19 and 21 were analysed by direct sequencing. Efficacy and tolerability were compared according to *EGFR* mutational status.

69 NSCLC patients with brain metastases were identified, 17 of whom harboured *EGFR* mutations. Objective response rate in patients with *EGFR* mutations was 82.4%; no responses were observed in unselected patients ($p<0.001$). Median (95% CI) time to progression within the brain for patients harbouring *EGFR* mutations was 11.7 (7.9–15.5) months, compared to 5.8 (5.2–6.4) months for control patients whose *EGFR* mutational status had not been assessed ($p<0.05$). Overall survival was 12.9 (6.2–19.7) months and 3.1 (2.5–3.9) months ($p<0.001$), respectively. The toxicity of erlotinib was as expected and no differences between cohorts were observed.

Erlotinib is active in brain metastases from NSCLC; this clinical benefit is related to the presence of activating mutations in exons 19 or 21 of the *EGFR* gene.

KEYWORDS: EGFR, metastases, mutation screening, nonsmall cell lung cancer, targeted therapy

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Lung cancer is the leading cause of cancer-related death worldwide. Brain metastases from nonsmall cell lung cancer (NSCLC) are present in 20–30% of patients [1] and are associated with a poor prognosis despite treatment with whole brain radiotherapy (WBRT), with a median survival of <6 months [2]. Apart from WBRT, few treatment options are currently available for these patients.

Tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR) are novel treatment options for advanced NSCLC, with a reported response rate of 9% in an unselected non-chemotherapy-naïve population [3]. Activating *EGFR* mutations within the tyrosine kinase (TK) domain are found to be highly associated with sensitivity to the EGFR TKIs gefitinib or erlotinib in advanced NSCLC [4–6]. Almost 90% of all known mutations in the TK domain of the *EGFR* gene are located in exon 19 (in-frame deletion of the conserved sequence LREA) or in exon 21 (L858R point mutation). Recent studies have shown that these *EGFR* mutations are highly oncogenic in transgenic mice and maintenance of the lung tumours in these mice is dependent on continued expression of the *EGFR* mutants [7, 8]. These data suggest that NSCLC expressing *EGFR* mutants is itself a different molecular entity [9, 10].

Although individual case reports of patients achieving objective responses to erlotinib or gefitinib have been published, the role of TKIs in patients with brain metastases remains unclear. To address this issue, we retrospectively evaluated the efficacy of erlotinib in a series of patients with brain metastases from NSCLC and its association with the presence of activating mutations in the *EGFR* gene. Safety was evaluated as a part of the analysis.

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MATERIALS AND METHODS

Patients

We retrospectively evaluated patients with NSCLC and metastatic dissemination to the brain, who had been registered in the Spanish Lung Adenocarcinoma Data Base Study (SLADB) from April 2005 to May 2006. The SLADB is a large database sponsored by the Spanish Lung Cancer Group (SLCG), whose aim was to evaluate the feasibility of large-scale screening for *EGFR* mutations in NSCLC patients and to examine the association between the mutations and the outcomes of the treatment with erlotinib. Primary tumour biopsy specimens from 2,105 NSCLC patients were analysed [11] and only those harbouring *EGFR* mutations were included in the database.

In addition, in order to have a control population of patients with brain metastasis from lung cancer, we consulted the TargeT study database and picked patients with brain metastasis enrolled during the same time period whose *EGFR* mutational status was either unknown or wild-type. The TargeT study is a Spanish nonrandomised phase II trial evaluating the efficacy and safety of first- and second-line erlotinib in patients with histologically confirmed stage IIIB or IV NSCLC. Erlotinib was given at a daily dose of 150 mg until disease progression or severe toxicity.

Both the SLADB and the TargeT study were approved by the corresponding institutional review boards and patients provided written informed consent prior to enrolment.

Efficacy and safety

Assessment of treatment efficacy at the brain level was periodically performed by brain magnetic resonance imaging or computed tomography (CT) scan, according to the clinical practice of each site. Lung tumour response was evaluated by CT scan. Liver or bone metastases, if present, were evaluated by upper abdominal CT scan and bone scan, respectively. Efficacy is reported in terms of objective response rate according to the Response Evaluation Criteria in Solid Tumours [12], time to progression (TTP) and overall survival (OS). TTP of the intracranial lesions was measured from the date of first erlotinib intake until the date of progression within the brain or last follow-up. OS was measured from the date of first erlotinib intake until death or last survival follow-up. Safety data consists of the adverse events related to erlotinib according to the National Cancer Common Toxicity Criteria version 3 grading system [13].

EGFR mutation analysis

The analysis of *EGFR* mutations was performed at the central laboratory of the SLCG at the Catalan Institute of Oncology (Hospital Germans Trias i Pujol, Badalona, Spain). EGFR mutations in exons 19 and 21 were analysed as described previously [11]. For more details on genetic analysis see the online supplementary data S1.

Statistical analysis

Patient characteristics are listed by their frequencies for qualitative variables and by median values and ranges for quantitative variables. Differences among response rates were analysed by the Chi-squared test or Fisher's exact test, as appropriate. Actuarial progression and survival curves were generated using the Kaplan–Meier method. The log-rank test was used to detect differences between subgroups. Two-sided p-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS for Windows version 13.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient and tumour characteristics

This retrospective analysis includes 69 patients with NSCLC metastatic to the brain, whose main baseline and clinical characteristics are summarised in table 1. Most of the patients were current or former smokers (68.0%), with adenocarcinoma (68.0%) and an Eastern Cooperative Oncology Group performance status of one (61.5%). 37 (53.6%) patients were male.

Of the 69 patients with brain metastases, 17 (24.6%) harboured mutations in the *EGFR* gene. An in-frame deletion in exon 19 (E746-A750) was found in 12 (70.6%) patients, while a point mutation in exon 21 (L858R) was detected in the remaining five (29.4%) patients. The majority of patients with *EGFR* mutations were female (64.7%), never-smokers (64.7%) and had adenocarcinomas (82.4%).

In contrast, the 52 control cases (75.4% of the whole series) from the TargeT study were unselected patients, whose *EGFR* mutational status had not been assessed (50 patients) or had confirmed wild-type *EGFR* gene (two cases); these control patients were mainly males (59.6%) and former or current smokers (78.8%); adenocarcinoma was also the predominant histology in this group (63.5%).

Of the entire series, 55 patients were treated with standard WBRT prior to erlotinib treatment: nine (16.4%) patients with *EGFR* mutation and 46 (84.6%) in the control group. Approximately half (47.1%) of the patients with *EGFR* mutations did not receive WBRT, and oral erlotinib was the sole treatment. In contrast, all control patients with available data of treatment had received erlotinib plus radiotherapy. Median (range) time from the end of WBRT treatment until the beginning of erlotinib intake was 42 (9–270) days. None of the patients received stereotactic radiation or underwent resection of the brain lesions.

Nine (52.9%) of the 17 patients harbouring *EGFR* mutations and 23 (44.2%) control cases received chemotherapy after erlotinib treatment failure.

Treatment efficacy

Response was not evaluable in 16 patients due to early death; 53 patients were evaluable for response. 14 (26.4%) patients attained an objective response in the brain lesions. All of them harboured mutations in the *EGFR* gene. Three patients with *EGFR* mutations had stabilisation of the intracranial lesions. Therefore, the objective response rate in the subgroup of evaluable patients with *EGFR* mutations was 82.4%, with complete resolution of the brain metastases in eight cases (47.1%) and partial response in six (35.3%).

No objective response within the brain was reported among patients in the control cohort, even though they had all received WBRT. Difference in response rate between patients with *EGFR* mutations and unselected control patients was statistically significant ($p<0.001$; table 2). Remarkably, however, 77.8% of

TABLE 1 Baseline patient characteristics

Characteristics	All patients	Cases with *EGFR* mutations	Control cases
Subjects	69 (100)	17 (24.6)	52 (75.4)
Sex			
Male	37 (53.6)	6 (35.3)	31 (59.6)
Female	32 (46.4)	11 (64.7)	21 (40.4)
Age yrs	55 (26–81)	56 (26–70)	55 (39–81)
Smoking history			
Never-smokers	22 (32.0)	11 (64.7)	11 (21.2)
Former or current smokers	47 (68.0)	6 (35.3)	41 (78.8)
Histology			
Adenocarcinoma	47 (68.0)	14 (82.4)	33 (63.5)
Large-cell carcinoma	15 (21.7)	2 (11.8)	13 (25.0)
Bronchioloalveolar carcinoma	1 (1.5)	1 (5.8)	0
Squamous cell carcinoma	6 (8.7)	0	6 (11.5)
ECOG PS			
0	9 (13.0)	1 (5.8)	8 (16.3)
1	40 (58.0)	10 (58.8)	30 (61.2)
2	14 (20.2)	5 (29.4)	9 (18.4)
3	2 (2.9)	0	2 (4.1)
Unknown	4 (5.8)	1 (5.8)	3 (5.7)
Erlotinib treatment line			
1st	26 (37.7)	10 (58.8)	16 (30.8)
2nd	20 (29.0)	5 (29.4)	15 (28.8)
3rd	23 (33.3)	2 (11.8)	21 (40.4)
Extracranial metastases			
Yes	45 (65.2)	10 (58.8)	35 (67.3)
No	24 (34.8)	7 (41.2)	17 (32.7)
WBRT			
No	8 (11.6)	8 (47.1)	0
Yes	55 (79.8)	9 (52.9)	46 (88.4)
Unknown	6 (8.7)	0	6 (11.6)
Post-erlotinib chemotherapy			
Yes	32 (46.4)	9 (52.9)	23 (44.2)
No	37 (53.6)	8 (47.1)	29 (55.8)
***EGFR* mutation**			
Exon 19 deletion	12 (17.4)	12 (70.6)	
Exon 21 L858R	5 (7.2)	5 (29.4)	

Data are presented as n (%) or median (range). Data for the entire series, for those patients harbouring an *EGFR* gene mutation and for control cases are shown. *EGFR*: epidermal growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group performance status; WBRT: whole brain radiotherapy.

patients with the unknown *EGFR* mutational status showed stabilisation of the brain disease after treatment with WBRT plus erlotinib.

In the subgroup of patients with *EGFR* mutations, eight (47%) patients did not receive WBRT and erlotinib was the only treatment; of those, six (75%) achieved an objective response (complete response and partial response) (table 3). A representative case of brain response to erlotinib (case number 5) is shown in figure 1. All patients but one receiving erlotinib plus WBRT showed response of the intracranial disease (table 3).

In addition to the efficacy within the brain, the response of the primary tumour and extracranial metastases (if present) was also evaluated in the subgroup of patients with activating *EGFR* mutations (table 3). All patients with *EGFR* mutations showed tumour response or disease stabilisation. All patients but one achieving an objective response of the intracranial lesions also attained a response in the extracranial locations. Two of the three patients with stable disease in the brain attained a partial response in the primary tumour as well as in the extracranial metastases. One patient had stable disease at both the thoracic and brain levels.

Median (95% CI) time to progression in the brain for the entire series was 2.9 (2.3–3.5) months. Patients harbouring *EGFR* mutations had a median (95% CI) TTP within the brain of 11.7 (7.9–15.5) months, compared to 5.8 (5.2–6.4) months in the control cohort ($p<0.05$) (fig. 2a). Of the 13 progressing patients harbouring *EGFR* mutations, six experienced disease progression

TABLE 2 Response of brain metastases in patients treated with erlotinib

	All patients	Cases with *EGFR* mutations	Control cases
Patients n	53	17	36
CR	8 (15.1)	8 (47.1)	0
PR	6 (11.3)	6 (35.3)	0
CR+PR	14 (26.4)	14 (82.4)	0
SD	31 (58.5)	3 (7.6)	28 (77.8)
PD	8 (15.3)	0	8 (22.2)

Data are presented as n (%), unless otherwise stated. Data for the entire series, for those patients harbouring *EGFR* gene mutations and for control cases are shown. EGFR: epidermal growth factor receptor; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

in the primary lung lesions, four within the brain and three in the liver (table S1 in the online supplementary material).

Median (95% CI) OS for the entire population was 4.3 (2.3–6.2) months. Patients harbouring *EGFR* mutations had a median OS of 12.9 (6.2–19.7) months while the control group showed a median (95% CI) OS of 3.1 (2.5–3.9) months ($p<0.001$) (fig. 2b). 1-yr survival was 69% in those patients with mutations and 9% in the unselected population ($p<0.001$) (table S2 in the online supplementary material).

No differences in response rate, TTP within the brain and OS were found according to performance status and treatment line (data not shown) among patients harbouring *EGFR* mutations, but the small population does not allow definitive conclusions.

Treatment toxicity

The most common side-effects of erlotinib were rash and diarrhoea. Skin disorders occurred in 37 (53.6%) cases. Grade $\geqslant 3$ skin toxicity, including desquamative lesions, pruritus, acne, conjunctivitis and alopecia were more frequent in patients with *EGFR* mutations (18.7%) than in the control cases (11.5%), although this difference did not reach statistical significance ($p=0.17$). The initial dose of erlotinib was reduced to 100 mg a day in five patients with grade 3 skin toxicity. This measure was sufficient to decrease the skin toxicity to grade 2. Gastrointestinal toxicity was mild. 17 (25%) of the 69 patients experienced some gastrointestinal symptom. Grade 3–4 diarrhoea was reported in 4% of patients in the control group, whereas none of the patients with *EGFR* mutations developed severe diarrhoea.

DISCUSSION

This retrospective study shows that the EGFR TKI erlotinib is active in patients with brain metastases from NSCLC. We have observed an overall response rate of 26.4% in a series of 69 NSCLC patients with metastatic dissemination to the brain treated either with WBRT plus erlotinib or erlotinib alone. Disease control was achieved in an impressive 84.9% of the patients. We have also identified a group of patients with brain metastases in whom erlotinib is particularly active. Those patients harbouring activating mutations in the EGFR TK domain attained an objective response rate of 82.4%, in some cases with highly dramatic complete responses (47.1%). In contrast, unselected patients, whose *EGFR* mutational status

TABLE 3 Tumour response by site among patients harbouring *EGFR* mutations

Patient	Disease sites			Prior WBRT
	Brain metastases	Primary tumour	Extracranial metastases	
1	CR	PR	CR	No
2	PR	PR	No ECM	Yes
3	SD	PR	PR	No
4	CR	PR	CR	No
5	CR	PR	No ECM	No
6	SD	PR	PR	No
7	PR	PR	PR	Yes
8	CR	PR	PR	Yes
9	CR	PR	No ECM	No
10	PR	CR	PR	No
11	CR	PR	NE	Yes
12	PR	CR	CR	Yes
13	PR	SD	No ECM	Yes
14	CR	CR	No ECM	Yes
15	PR	PR	No ECM	No
16	SD	SD	No ECM	Yes
17	CR	PR	CR	Yes

Data of response to treatment of the primary lung tumour, brain metastasis and extracranial metastases are shown. Whole brain radiotherapy (WBRT) is listed for each patient. EGFR: epidermal growth factor receptor; CR: complete response; PR: partial response; NE: not evaluable; SD: stable disease; ECM: extracranial metastases.

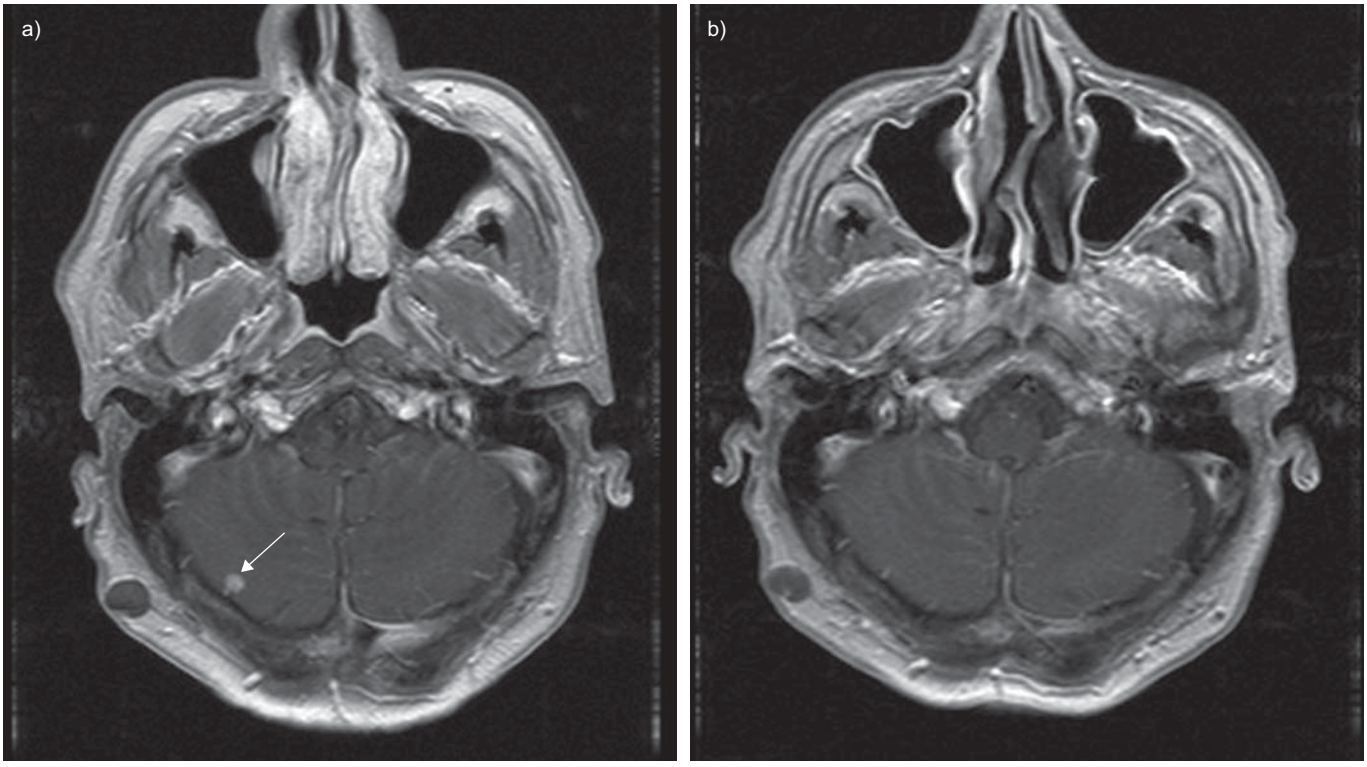

FIGURE 1. Brain magnetic resonance imaging. Axial T1-weighted image after contrast (Gd) administration of patient 5, a male with adenocarcinoma of the lung and a brain metastasis, harbouring exon 19 deletion. a) A brain metastasis in the right hemisphere of the cerebellum before initiating erlotinib (white arrow). A sebaceous cyst is seen into the right subcutaneous tissue. b) Complete response of the cerebellum metastasis after 4 months of treatment with erlotinib.

was either unknown or wild-type, showed no objective responses, even though disease control occurred in 77.8% of the population. A significant difference in TTP within the brain lesions and in OS was also observed according to *EGFR* mutational status. TTP within the brain for patients harbouring *EGFR* mutations (11.7 months) was twice that for unselected patients (5.8 months). Furthermore, patients harbouring *EGFR* mutations had four-fold longer OS (12.9 months) than those patients in the control group (3.1 months). 1-yr survival (69%) for patients with mutations was particularly remarkable, since median OS in unselected patients with lung cancer metastatic to the brain is normally <6 months after conventional therapy [2]. Median TTP for patients with the mutated *EGFR* gene was of similar magnitude to that described in larger series with erlotinib. In a recent prospective study with erlotinib, reported median progression-free survival was 14 months [11], and in a pooled analysis examining five studies of first-line treatment with erlotinib or gefitinib in patients in whom *EGFR* mutational status was analysed, median progression-free survival for those patients harbouring activating mutations was 11.8 months [14]. By contrast, median OS in our series was shorter than that reported by other authors. This result could be partly due to a shorter follow-up in our study, but it also may reflect the worse prognosis of those patients with brain metastasis and the modest results yielded by other therapeutic approaches, thus underlining the benefit provided by erlotinib. In the work from ROSELL and co-workers [10, 11] treatment with erlotinib reached a median (95% CI) progression-free survival of 14 (11.3–16.7) months for patients without brain metastases and 10 (5.6–14.4) months for those with brain metastases (p=0.31). Median (95% CI) survival was 28 (21.5–34.4) months for patients without brain metastases and 18 (4–31.9) months for patients with brain metastases (p=0.008) (see appendix in the online supplementary material) [11].

Several reports support that stereotactic radiosurgery, Gamma Knife or linear accelerator, with or without WBRT, are interesting local therapeutic approaches for a limited number of small brain metastases and good prognosis. However, most cases require a systemic approach to provide a treatment for the extracranial disease [15]. It has been suggested that *EGFR* mutations confer radiosensitivity *in vitro* [16], and recently GOW *et al.* [17] have concluded that the presence of *EGFR* mutations is an independent predictor of response to WBRT in brain metastases of lung adenocarcinoma. The impact of erlotinib on brain metastases might thus have been masked by the effects of radiation therapy to the brain. However, our study clearly shows that those patients with brain metastases and *EGFR* mutations are better responders to erlotinib, whether or not they had received previous WBRT. All patients with *EGFR* mutations obtained benefit within the brain (82.4% with objective response and 7.6% with stable disease as the best response), and 47.1% attained a complete remission of the cerebral lesions. Interestingly, six (42.9%) of the 14 patients with *EGFR* mutations achieving objective tumour response had not received brain radiation therapy, and four of these six attained a complete remission of brain lesions. This finding strongly supports the role of erlotinib in the response of the brain metastases.

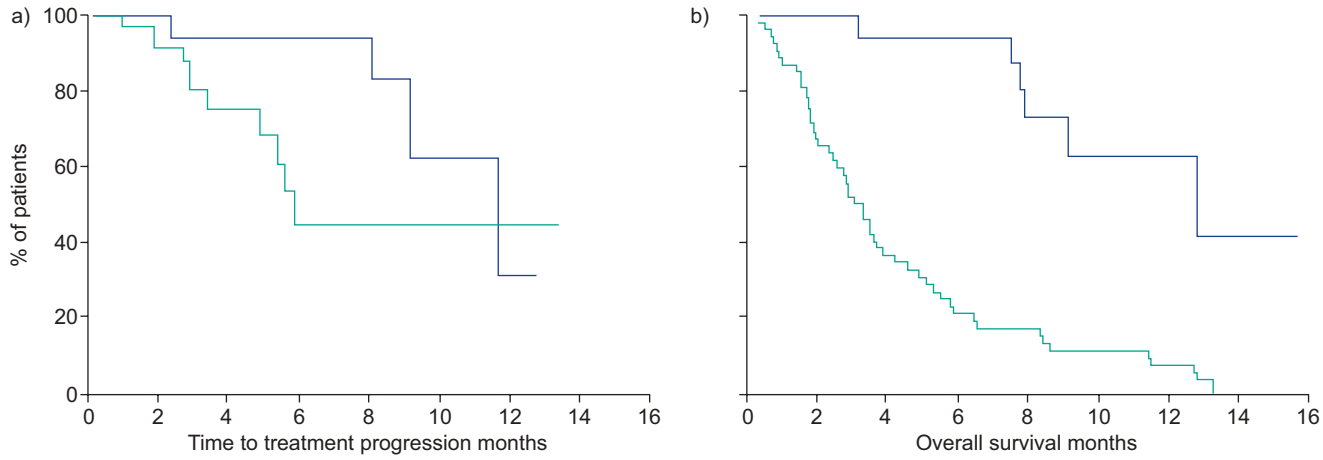

FIGURE 2. a) Median time to progression (TTP) in the brain. Patients harbouring *EGFR* mutations (blue line) had a median (95% CI) TTP within the brain of 11.7 (7.9–15.5) months, compared to 5.8 (5.2–6.4) months in the control cohort (green line) ($p<0.05$). b) Median overall survival (OS). Patients harbouring *EGFR* mutations (blue line) had a median (95% CI) OS of 12.9 (6.2–19.7) months while the control group (green line) showed a median OS of 3.1 (2.5–3.9) months ($p<0.001$). In the control groups the *EGFR* mutational status was either unknown or wild-type.

Moreover, the efficacy of erlotinib in brain metastases was paralleled by its efficacy in the lung primary lesions and in other metastatic sites. All patients with *EGFR* mutations responding to treatment within the brain also responded in the extracranial lesions. In fact, brain lesions seem to be more sensitive to erlotinib than thoracic tumours: eight patients with complete responses within the brain, four of whom were treated only with erlotinib, attained partial responses in their primary tumours. Therefore, we can conclude that erlotinib is active both in brain metastases and in lung primary lesions and other metastatic sites more accessible than the brain.

In the present study, there was a difference in the number of treatment lines between patients with *EGFR* mutations and patients with unknown *EGFR* mutational status; unselected patients were more likely to have received previous therapies. While this could account for differences in outcomes between the two groups of patients, 41.2% of patients with *EGFR* mutations received erlotinib as a second or further line of treatment, and median TTP in this subgroup remained longer than 11 months. Moreover, among patients harbouring *EGFR* mutations, no significant differences in response rate, TTP within the brain and OS were detected according to line of treatment and performance status, but these data should be cautiously interpreted due to the small size of the subgroups.

Our findings support the hypothesis that erlotinib is able to cross the blood–brain barrier and displays efficacy against intracranial metastasis. In the past, the response of malignancies involving the brain has been anecdotal [18], which might reflect the absence of active medical treatments, rather than the refractoriness of brain lesions to all forms of therapy. We have previously reported that tamoxifen, which is usually regarded as ineffective in breast cancer involving the brain, induced a complete response in a patient with brain metastases from breast cancer [19].

The results observed in the present series of patients with brain metastases confirm other isolated reports of the efficacy of EGFR TKIs [20–24]. Gefitinib has been reported to be active in a series of patients with brain metastases [21–24], most of them Asiatic, although a high incidence of recurrence at the brain level after treatment with gefitinib has also been addressed [25]. In a prospective trial, CERESOLI *et al.* [24] showed efficacy of gefitinib on brain metastases from 41 patients with NSCLC, with a median overall survival of 5 months. None of the mentioned studies selected the patients for treatment according to the mutational status of the *EGFR* gene, or carried out this analysis. It has been pointed out that gefitinib may have an incomplete penetration though the blood–brain barrier [26] and its effectiveness for the treatment of brain metastasis may depend on the disruption of the barrier [27].

Finally, the tolerability of oral TKIs in patients with brain metastases has not been specifically addressed before, although this is particularly relevant in the case of oral drugs. Erlotinib was well tolerated overall in patients with brain metastases, with skin toxicity and diarrhoea as the most common adverse events. Skin toxicity has been associated with clinical benefit to erlotinib, but its relationship with *EGFR* mutations has not been evaluated [28]. In the present study, a nonsignificant trend towards more severe skin toxicity in patients with *EGFR* mutations was observed.

In conclusion, erlotinib is well tolerated and active against brain metastases in NSCLC patients. The routine assessment of *EGFR* mutations in NSCLC patients with intracranial lesions is warranted.

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STATEMENT OF INTEREST

A statement of interest for the present study can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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