

Development of Central Nervous System Metastases in Patients with Advanced Non–Small Cell Lung Cancer and Somatic *EGFR* Mutations Treated with Gefitinib or Erlotinib

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Abstract

Purpose: Gefitinib and erlotinib can penetrate into the central nervous system (CNS) and elicit responses in patients with brain metastases (BM) from non–small cell lung cancer (NSCLC). However, there are incomplete data about their impact on the development and control of CNS metastases.

Experimental Design: Patients with stage III/IV NSCLC with somatic *EGFR* mutations initially treated with gefitinib or erlotinib were identified. The cumulative risk of CNS progression was calculated using death as a competing risk.

Results: Of the 100 patients, 19 had BM at the time of diagnosis of advanced NSCLC; 17 of them received CNS therapy before initiating gefitinib or erlotinib. Eighty-four patients progressed after a median potential follow-up of 42.2 months. The median time to progression was 13.1 months. Twenty-eight patients developed CNS progression, 8 of whom had previously treated BM. The 1- and 2-year actuarial risk of CNS progression was 7% and 19%, respectively. Patient age and *EGFR* mutation genotype were significant predictors of the development of CNS progression. The median overall survival for the entire cohort was 33.1 months.

Conclusions: Our data suggest a lower risk of CNS progression in patients with advanced NSCLC and somatic *EGFR* mutations initially treated with gefitinib or erlotinib than published rates of 40% in historical series of advanced NSCLC patients. Further research is needed to distinguish between the underlying rates of developing CNS metastases between NSCLC with and without *EGFR* mutations and the impact of gefitinib and erlotinib versus chemotherapy on CNS failure patterns in these patients.

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Lung cancer remains the leading cause of cancer mortality in both men and women in the United States (1). Approximately 85% of these cancers are non–small cell lung cancer (NSCLC) (2). Despite recent advances in the treatment of patients with NSCLC, central nervous system (CNS) involvement remains a frequent complication leading to impaired quality of life and shortened survival.

Platinum-based combination chemotherapy has been the standard first-line treatment of patients with advanced NSCLC, resulting in response rates of 20% to 35% and median survival of 8 to 12 months (3, 4). Phase

III trials of cytotoxic chemotherapy for stage IV NSCLC have commonly included the frequency of brain metastases (BM) at the time of initiating systemic therapy but have seldom included data on the rates of CNS progression during the trial. Patients with stage III NSCLC do not have BM at the time of diagnosis and have a longer median survival, with 20% to 35% of patients alive at 2 years (5). This leads to a longer period in which patients can be observed for the development of CNS relapse. Therefore, the incidence of BM has been extensively reported in studies of patients with stage III NSCLC treated with systemic chemotherapy plus chest irradiation and/or surgical resection as part of a multimodality approach. These studies report a 40% to 55% incidence of CNS failure following definitive therapy for stage III NSCLC after a median follow-up of 35 to 37 months (6, 7). Authors have also suggested an increase in the incidence and relative importance of BM as the ultimate cause of treatment failure because of prolonged extracranial cancer control and longer survival (7).

Gefitinib and erlotinib are small-molecule reversible inhibitors of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) that have shown efficacy in patients with relapsed NSCLC and as initial therapy for

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Translational Relevance

Central nervous system (CNS) metastases remain a frequent complication in non-small cell lung cancer (NSCLC), and their occurrence has been altered little by conventional cytotoxic chemotherapy. The impact of epidermal growth factor receptor (*EGFR*) mutations and treatment with the *EGFR* tyrosine kinase inhibitors, gefitinib and erlotinib, on the outcome of CNS progression in NSCLC remains an area of investigation. We retrieved information on the clinical presentation and course of our patients with advanced NSCLC and somatic *EGFR* mutations initially treated with gefitinib or erlotinib to assess the risk of CNS progression. On the basis of the findings presented here, clinicians can gain a better understanding of the patterns of CNS failure and long-term outcomes in this patient population and get an estimation of the impact of specific patient and tumor-related factors on the development of CNS progression.

patients with advanced NSCLC and sensitizing *EGFR* mutations (8, 9). Most somatic *EGFR* mutations are in exons 18 through 21 of the tyrosine kinase domain and are associated with 60% to 80% response rates in patients treated with gefitinib or erlotinib (10). Studies of genotype-directed, first-line treatment of advanced NSCLC with gefitinib or erlotinib have shown time to progression of 10 to 12 months and median survival of 20 to 30 months among patients carrying sensitizing *EGFR* mutations (8, 11). Therefore, information is needed to assess whether the prolonged survival observed in NSCLC patients with somatic *EGFR* mutations translates into an increased cumulative risk of CNS progression.

In addition, there is incomplete data about the impact of gefitinib and erlotinib on the development and control of CNS metastases because these drugs can cause regression of established BM and may therefore delay the onset of CNS involvement. Prospective reports have shown that gefitinib and erlotinib can cause responses in 10% to 30% of patients with BM caused by metastatic NSCLC (12, 13). Intracranial response rates of 70% have also been reported among never-smoking, treatment-naive patients with lung adenocarcinoma and synchronous BM (14). Moreover, investigators from our center have shown that patients with leptomeningeal disease treated with up to 1,000 mg of gefitinib per day can achieve cerebrospinal fluid (CSF) gefitinib concentrations that can cause inhibition of growth of NSCLC with sensitizing *EGFR* mutations (15). However, concerns have also been raised about a high rate of CNS progression following systemic response to *EGFR* tyrosine kinase inhibitors (TKI). In a published series of 21 patients with advanced NSCLC who achieved a partial response to treatment with gefitinib, the crude rate of CNS progression reached 43% after a median follow-up of 27 months (16).

Six years have passed since the discovery and subsequent routine characterization of *EGFR* in our patients with NSCLC. Therefore, we retrieved information on the clinical presentation and course of our patients with advanced NSCLC and somatic *EGFR* mutations initially treated with gefitinib or erlotinib to assess the rate of CNS progression. We focused our analysis on the 1- and 2-year actuarial risk of CNS progression, as previous reports have suggested that most recurrences within the brain occur within 2 years of the initial diagnosis of NSCLC (17). The patients presenting with BM prior to the initiation of gefitinib or erlotinib were compared with patients without preexisting CNS involvement. In addition, the NSCLC patients with somatic *EGFR* mutations treated with gefitinib or erlotinib can be compared with the patients with similar characteristics treated with chemotherapy reported in the literature. If it seems that the frequency is less, studies can be undertaken to assess the outcome of NSCLC patients with *EGFR* mutations treated with chemotherapy. This will help to determine whether the difference in the frequency of CNS metastases between patients with somatic *EGFR* mutations is caused by a different underlying biological behavior of these tumors or whether the lower frequency is likely caused by the treatment with gefitinib or erlotinib. Finally, we examine prognostic factors on the outcome of CNS progression in this cohort of patients.

Patients and Methods

Study design and patients

Patients eligible for this study included those with stage IIIB or IV NSCLC (AJCC 6th edition) or patients with stage I–IIIA NSCLC with systemic relapse and somatic *EGFR* mutations who were treated with gefitinib or erlotinib as their initial systemic therapy for advanced NSCLC (18). Patients who were started on treatment with gefitinib or erlotinib from January 1, 2002, to February 1, 2009, were included in this analysis to allow at least 1 year of potential follow-up.

Patients were identified through a query of patient information for subjects prospectively enrolled in the Clinical Research Information System (CRIS) within the Lowe Center for Thoracic Oncology at the Dana-Farber Cancer Institute that tracks all of the patients referred for *EGFR* sequencing from our center. This patient information has been used for previous reports (19, 20). The patients included in this analysis represent 14% of the total patients with advanced NSCLC enrolled into our institution's CRIS database during the 7 years of the study. Four additional *EGFR* mutation-positive patients who had met all of these eligibility criteria were reported by investigators from the Beth Israel Deaconess Medical Center. These 4 patients represent all of the eligible patients from that institution and 7% of the total patients with advanced NSCLC who underwent screening for *EGFR* mutations at that center during the years of the study. Three of these patients have been studied and included in prior publications (19, 21).

Patients provided written informed consent for the collection of baseline clinical information, analysis of their tumor specimens, and collection of clinical outcomes information.

Forty-five patients included in this study were enrolled in prospective trials of gefitinib or erlotinib in previously untreated patients with advanced NSCLC, including 4 patients who participated in a phase II randomized study of erlotinib with or without carboplatin and paclitaxel in treatment-naïve subjects with lung adenocarcinoma who never smoked or were former light smokers; 2 patients were randomized to each arm (21–25).

The collection of clinical information on patients with somatic *EGFR* mutations was approved by the local institutional review board at Dana-Farber Cancer Institute and Beth Israel Deaconess Medical Center.

Mutation analysis

Tumor specimens for each patient on this study were obtained from diagnostic or surgical procedures. Samples consisted of either frozen tumor specimens or paraffin-embedded material. *EGFR* exons 18 to 21 were amplified by PCR and analyzed bidirectionally by direct sequencing for the presence of somatic mutations according to previously described methods (26, 27). Mutations were confirmed by multiple independent PCR amplifications, using criteria that have been previously reported (26). Any confirmed somatic *EGFR* mutation was sufficient to allow inclusion in this study.

Statistical methods

Baseline clinical characteristics were determined by prospective collection from a patient-administered questionnaire, including age at diagnosis, gender, patients' self-identified ethnic group, baseline Eastern Cooperative Oncology Group (ECOG) performance status at the start of treatment with gefitinib or erlotinib assessed by the health care provider, smoking status, tumor histology, prior therapy for patients with relapsed disease, start of systemic therapy, date of diagnosis of CNS involvement, treatment of BM prior to the initiation of first-line targeted therapy, type of somatic *EGFR* mutation, and the *EGFR*-TKI administered (gefitinib or erlotinib). Smoking status was categorized as current (smoked within 1 year prior to start of therapy), former (quit ≥ 1 year prior to start of therapy), or never (<100 lifetime cigarettes). Tumor histology was classified using WHO criteria (28).

Data were collected on the prevalence, incidence, and time to development of brain and leptomeningeal metastases in the 100 eligible, assessable patients from the start of treatment with gefitinib or erlotinib. All patients had undergone brain imaging at the time of initial diagnosis of NSCLC and/or at the recognition of advanced disease. Subsequent brain imaging was obtained in patients with symptoms or signs suggesting CNS involvement. Patients were most frequently evaluated by contrast-enhanced cranial MRI, although in some cases, a contrast-enhanced computed tomographic (CT) scan of the head was obtained

instead of an MRI. In many cases, the identification of brain metastases was followed by CT scans of the chest and abdomen to evaluate for other sites of metastatic disease. Positron emission tomographic scans were not routinely obtained for restaging purposes following the development of CNS metastases.

CNS metastases included all cases of parenchymal brain lesions and cytologically or radiographically diagnosed leptomeningeal disease. Radiographic findings indicative of leptomeningeal involvement included enhancement and/or enlargement of cranial nerves, nodular or linear leptomeningeal enhancement extending into sulci or basal cisterns, and intradural extramedullary enhancing nodules (29). CNS progression included both newly developed CNS metastases and progression of preexisting brain lesions. The crude risk of CNS progression was calculated as the sum of patients with newly developed brain or leptomeningeal metastases or progression of their preexisting CNS involvement divided by the number of patients treated. The actuarial risk of CNS progression was estimated using the cumulative incidence function in the presence of death as a competing risk. The pointwise 95% confidence interval (CI) was constructed using the asymptotic variance estimator of Aalen (30) with a $\log(-\log)$ transformation, following the approach of Choudhury (31). Time to progression and overall survival were estimated using the Kaplan–Meier product-limit method and were calculated from the first-day treatment with gefitinib or erlotinib was initiated. The outcome was censored if a patient had not progressed or died at the time of last follow-up.

Gray's test was used in the univariate analysis of potential prognostic factors on the outcome of CNS progression (32). The variables considered included age cutoff at the median (≤ 63 vs. >63), gender, race (White, non-Hispanic vs. Asian), smoking status (never vs. former smoker), histology [predominant bronchioloalveolar carcinoma (BAC) vs. non-BAC adenocarcinoma vs. other histologic subtypes], ECOG performance status at the start of gefitinib or erlotinib (0–1 vs. ≥ 2), initial stage (relapsed NSCLC vs. advanced NSCLC at presentation), type of *EGFR* mutation (exon 19 deletions vs. L858R vs. other), and *EGFR*-TKI administered (gefitinib vs. erlotinib). Competing risks regression using the proportional subdistribution hazards model of Fine and Gray was used for multivariate analysis to control for the simultaneous effects of factors with independent prognostic significance (33). All *P* values are based on 2-sided hypothesis tests. The statistical analysis was computed using SAS 9.2 (SAS Institute Inc.) and the *cmprsk* package in R version 2.6.2 (R Found Stat Comput).

Power calculation

The anticipated crude risk of CNS progression in patients with advanced NSCLC treated with chemotherapy was estimated to be 40% on the basis of prior literature (7). With 100 *EGFR* mutation-positive patients, we would have at least 90% power to detect a decrease in the risk of CNS progression of 25% or less at a 2-sided 5% significance level.

Table 1. Baseline patient characteristics

Total, N	100
Gender	
Male	18
Female	82
Median age (range), y	63 (35–79)
Race	
White, non-Hispanic	83
Asian	15
Black	2
ECOG performance status	
0–1	92
≥2	8
Smoking status	
Never	61
Former	39
Histology	
Adenocarcinoma	89
Adenosquamous	2
Squamous	1
NSCLC NOS	8
Stage ^a	
Relapsed ^b	27
IIIB (without/with pleural effusion)	17 (5/12)
IV	56
Prior therapy for stages I–IIIA (n = 27)	
Surgery alone	13
Surgery and chemotherapy	4
Surgery and chest radiation therapy	1
Chemotherapy plus chest radiation	3
Chemotherapy, chest radiation, and surgical resection	6
Prior brain metastases	19
Prior therapy for brain metastases (n = 19)	
Radiation	15
Resection and radiation	2
None	2
EGFR-TKI	
Gefitinib	15
Erlotinib	85

Abbreviation: NOS, not otherwise specified.

^aAJCC Staging System, 6th edition.

^bPatients with stages I–IIIA with systemic relapse following definitive therapy.

included in the study. There were 82 women, and the median age of the study cohort was 63 years (range, 35–79 years). Sixty-one patients were never smokers. Eighty-nine patients had adenocarcinoma, and bronchioloalveolar features were present in 23 of them. Twenty-seven patients had previously undergone treatment for stage I–IIIA NSCLC that subsequently relapsed (10 patients with stage I, 11 patients with stage II, and 6 patients with stage IIIA). Fifty of the 100 patients had disease limited to the thorax at the start of treatment with gefitinib or erlotinib. Nineteen patients had parenchymal BM at the time of diagnosis of advanced NSCLC, before the initiation of gefitinib or erlotinib. Three of the 19 patients had a solitary BM on contrast-enhanced cranial MRI, whereas multiple BMs were observed in the other 16 cases. Fourteen of the 19 patients were treated with whole-brain radiation therapy (WBRT) to doses of 3,000 to 4,050 cGy; 2 of the 14 patients had also been treated with radiosurgery. A solitary BM was resected in 2 patients, followed by WBRT in 1 patient and stereotactic radiosurgery (SRS) to the surgical bed in the other. Another patient with 3 BMs was treated with SRS alone. The 2 remaining patients had asymptomatic BM measuring less than 1 cm and received no localized CNS therapy before their physicians elected to treat them with erlotinib.

Eighty-nine patients had a single somatic *EGFR* mutation. Table 2 summarizes the *EGFR* mutations identified. The most common mutations observed were in-frame exon 19 deletions (51 patients) and the exon 21 point mutation termed L858R (33 patients). A small number of other mutations were found, including 3 patients with exon 20 insertion/duplications that are not associated with sensitivity to treatment with gefitinib or erlotinib (34). Two additional patients had the point mutation T790M in exon 20, which has been correlated with the development of resistance to gefitinib and erlotinib in patients with sensitizing mutations who were initially responsive to the drug (35). Both patients also had concurrent sensitizing *EGFR* mutations (one patient had an exon 19 deletion, the other had *EGFR* L858R) and had a partial response to gefitinib for 23 and 27 months before showing evidence of disease progression that harbored both a sensitizing mutation and the T790M mutation. A pretreatment tissue specimen from these patients was either not available or contained insufficient tumor material for *EGFR* mutational analysis. Both patients underwent repeated tumor biopsies and characterization of *EGFR* after the development of progressive disease. In both cases, the resistant T790M mutation was presumed secondary and assumed not to be present before treatment with gefitinib was initiated.

Results

Patient characteristics

Between January 1, 2002, and February 1, 2009, 100 patients with stage IIIB/IV or relapsed NSCLC harboring a somatic *EGFR* mutation were treated with gefitinib or erlotinib as their initial therapy for advanced NSCLC. Table 1 shows the baseline characteristics of the patients

Patterns of disease progression

Forty-four of the 100 patients were alive at their last follow-up, and 56 patients have died. Eighty-four patients progressed after a median potential follow-up of 42.2 months (range, 12–95 months). The median time to progression for the entire cohort was 13.1 months (Fig. 1).

Table 2. Epidermal growth factor receptor somatic gene mutations identified

Exon	Amino acid change	Frequency, N
18	G719A ^a	2
	G719C ^b	2
19	Deletion ^c	51
	W731X	1
	L747P	1
	D761Y ^b	1
	I740T ^d	1
	K745_E746insTPVAIK ^d	1
	K739_I744dup	1
20	T790M ^{c,e}	2
	G779C ^{a,f}	2
	G779V ^f	1
	S768I ^b	1
	772_773dup	1
	V769_D770insASV	1
	D770delinsGI	1
21	L858R ^{e,g}	33
	V834L ^g	2
	L861Q ^{a,c}	6
	G873E ^c	1

Abbreviations: del, deletion; dup, duplication; ins, insertion.

^aOne patient had both G719A and L861Q; 1 patient had both G719A and G779C.

^bOne patient had both G719C and D761Y; 1 patient had both G719C and S768I.

^cOne patient had both an exon 19 deletion and T790M; 1 patient had all of G873E, L861Q, and an exon 19 deletion.

^dOne patient had both K745_E746insTPVAIK and I740T.

^eOne patient had both L858R and T790M.

^fOne patient had both G779C and G779V.

^gTwo patients had both L858R and V834L.

Of the 100 patients, 24 patients subsequently developed BM or progression of their previously existing CNS involvement. Eight of the patients had a history of previously treated BM whereas 16 did not. Eleven of the 19 patients with preexisting brain lesions had controlled intracranial disease after a median follow-up of 10.2 months (range, 1–31 months). Leptomeningeal metastases occurred in 8 patients; 6 diagnosed by MRI and cytologic examination of CSF and 2 by MRI only. Four of the 8 patients had synchronous BM at the time of diagnosis of leptomeningeal involvement, including 2 patients who were treated with WBRT before the initiation of gefitinib or erlotinib. The brain was the initial site of progression on gefitinib or erlotinib in 10 patients, and the sole site of initial failure in 5 of these 10 patients, including 3 patients with isolated leptomeningeal metastases without BM.

The overall crude incidence of CNS progression in the entire cohort was 28%. The 1- and 2-year actuarial risk of

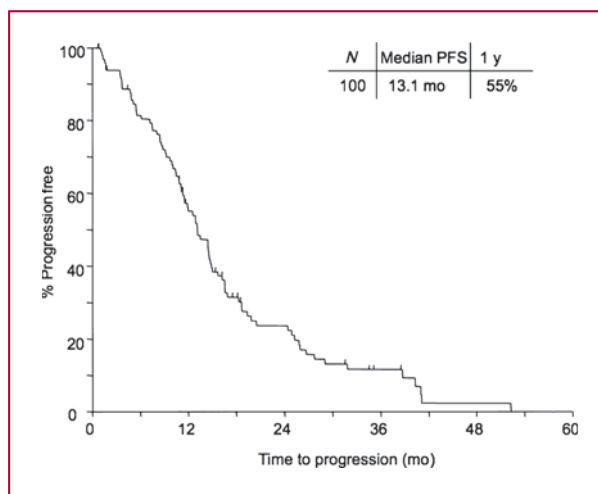


Fig. 1. Kaplan–Meier curve for progression-free survival (PFS) in all eligible patients.

CNS progression was 7% (95% CI, 3–13) and 19% (95% CI, 11–27), respectively (Fig. 2A). When the analysis was narrowed to only those 81 patients without preexisting BM, the 1- and 2-year actuarial rates of CNS failure were 6% (95% CI, 2–13) and 13% (95% CI, 7–22), respectively, compared with corresponding rates of 11% (95% CI, 2–30) and 47% (95% CI, 17–72) in 19 patients with preexisting CNS involvement ($P = 0.003$, Fig. 2B). The actuarial risk of leptomeningeal metastases in the entire cohort was 1% (95% CI, 0–5) and 6% (95% CI, 2–12) at 12 and 24 months, respectively. Prior CNS disease was associated with an increased risk of BM ($P < 0.001$) but not leptomeningeal involvement ($P = 0.233$). The impact of prior CNS involvement on the cumulative incidence of brain and leptomeningeal metastases is summarized in Table 3. The median time to development of CNS metastases relative to gefitinib or erlotinib initiation was 19.0 months (range, 1–64 months).

The median overall survival from the first-day treatment with gefitinib or erlotinib was initiated was 33.1 months (Fig. 3). The median survival times after the development or progression of BM or the diagnosis of leptomeningeal metastases were 5.5 and 5.1 months, respectively. Seven patients with CNS progression were alive at their last follow-up, after a median of 4.6 months following the development or progression of their CNS metastases (range, 3–65 months). Therapy with gefitinib or erlotinib was discontinued either prior to or shortly after the diagnosis of CNS failure in 26 of the 28 patients with CNS progression. Two patients underwent surgical resection of symptomatic BM that developed while receiving gefitinib therapy. One patient had enjoyed a response to gefitinib for 20 months before showing evidence of slow intrathoracic disease progression; therapy with gefitinib was continued. Metastatic disease in the brain developed 4 months later, treated with surgical resection and SRS to the surgical bed. Mutation analysis disclosed a sensitizing exon 19 deletion

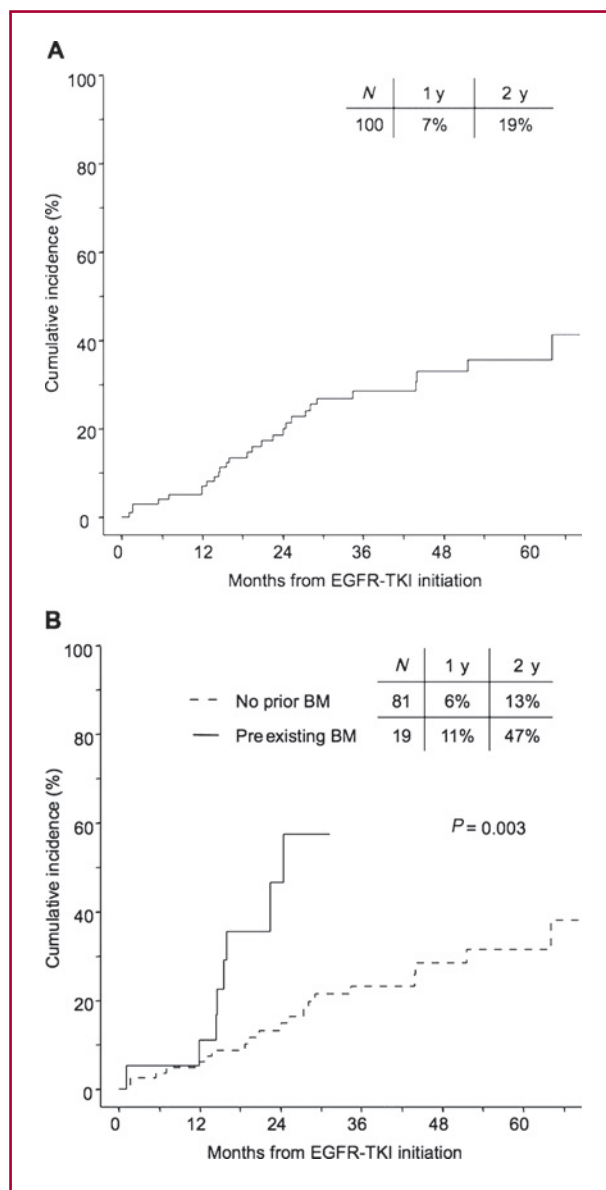


Fig. 2. Cumulative incidence of CNS progression in (A) all eligible patients and (B) patients with preexisting BM versus no prior BM.

concurrent with a T790M mutation in the brain tumor specimen. A paired sample from an extracranial site was not obtained. Another patient with brain-only relapse following definitive therapy for stage IIB lung adenocarcinoma had undergone resection of a parietal lobe lesion followed by SRS to the surgical bed and to a second brain lesion before initiating therapy with gefitinib. She subsequently suffered multiple brain-only progressions treated with localized CNS therapy, including resection of a symptomatic cerebellar metastasis that developed 37 months after the start of gefitinib. Molecular analysis detected an exon 20 insertion mutation in the brain tumor specimen, known to confer resistance to EGFR-TKI. The *EGFR* mutation status was not evaluated on a pretreatment specimen. She was

alive at her last follow-up and remained on gefitinib after 65 months without evidence of extracranial disease progression.

Predictors of brain relapse

We examined potential predictors of the development of CNS progression, using both univariate and multivariate analyses. The variables that reached statistical significance on univariate analysis were age and *EGFR* mutation genotype. Patients younger than 63 years had a 2-year actuarial risk of CNS progression of 27% versus 9% for older patients ($P < 0.001$). A higher 2-year actuarial risk of CNS progression was also observed among patients with exon 19 deletions and other *EGFR* mutations than among patients whose tumor harbored L858R (21% vs. 38% vs. 3%, respectively; $P = 0.029$). The effect of *EGFR* mutation genotype retained independent significance after multivariate analysis was used to control for the simultaneous effects of age and prior CNS involvement. The risk of CNS progression was almost triple among patients with exon 19 deletions (hazard ratio, 2.7; $P = 0.044$) and approximately 5 times higher among patients with other exon 18 to 21 mutations (hazard ratio, 5.7; $P = 0.021$) relative to *EGFR* L858R. The adjusted hazard ratio was 5.4 for patients younger than 63 versus older than 63 years ($P = 0.003$). The adjusted risk of CNS progression was 70% higher (hazard ratio, 1.7; $P = 0.290$) among patients with preexisting BM than among those without prior CNS involvement.

Discussion

In the current study, we report on the risk of CNS progression in patients with stage IIB/IV or relapsed NSCLC with somatic *EGFR* mutations who were treated with gefitinib or erlotinib as their initial therapy for advanced NSCLC. To our knowledge, this is the first published series to report on this outcome in patients with *EGFR* mutations, and it offers important insights into the patterns of CNS failure and long-term outcomes in this patient population. Consistent with prior reports, our patient characteristics reflect higher *EGFR* mutation frequencies among women, never smokers, and patients with adenocarcinoma (36).

Our analysis found that the crude incidence of CNS progression in patients with advanced *EGFR*-mutated NSCLC initially treated with gefitinib or erlotinib was 28% after a median potential follow-up of 42.2 months, whereas the 1- and 2-year actuarial risk of CNS progression was 7% and 19%, respectively. When the analysis was narrowed to only those patients without preexisting CNS involvement, the crude risk of CNS metastases was 20 of 81 (25%), whereas the 1- and 2-year actuarial risk of CNS progression was 6% and 13%, respectively. Previous studies in patients with stage III NSCLC have suggested a 40% to 55% crude incidence of overall CNS failure following definitive therapy after a median follow-up of 35 to 37 months (6, 7). Our results therefore suggest a lower

Table 3. Impact of prior CNS involvement on the cumulative risk of CNS progression

	1 y	2 y	P
CNS progression			
No prior BM (<i>n</i> = 81)	6%	13%	0.003
Preexisting BM (<i>n</i> = 19)	11%	47%	
Brain metastases ^a			
No prior BM (<i>n</i> = 81)	5%	9%	<0.001
Preexisting BM (<i>n</i> = 19)	11%	47%	
Leptomeningeal metastases			
No prior BM (<i>n</i> = 81)	1%	4%	0.233
Preexisting BM (<i>n</i> = 19)	0%	15%	

^aNewly developed BM or progression of preexisting brain lesions.

risk of CNS progression in patients with somatic *EGFR* mutations initially treated with gefitinib or erlotinib for advanced NSCLC than published rates of CNS failure in NSCLC patients treated with systemic chemotherapy plus local therapy for locally advanced disease. In addition, the development of CNS metastases was a relatively late event in our patients, occurring at a median of 19 months following the initiation of gefitinib or erlotinib. This compares favorably with reported median time to brain relapse of 9 to 13 months following the initiation of therapy in patients treated definitively for stage III NSCLC (6, 17). These findings are notable because the patients included in our series are enriched with known factors associated with a higher risk of CNS metastases, including advanced NSCLC stage and adenocarcinoma subtype (37).

One possible explanation for the lower risk of CNS progression observed in the current study is that we focused our analysis on a molecularly defined cohort of patients. There is evidence that the presence of *EGFR* mutations may have a favorable prognostic impact and may represent

more indolent tumor biology irrespective of systemic treatment (8, 9). It is therefore conceivable that tumors harboring *EGFR* mutations produce BM less frequently than nonmutated tumors. However, published data are thus far too limited to draw any firm conclusion. For example, results from a retrospective surgical series of 117 patients suggested that isolated recurrence in the brain following definitive surgical resection of pulmonary adenocarcinoma was more frequent in patients with tumors bearing *EGFR* mutations (mutated *EGFR* vs. wild-type, 24% vs. 9%; *P* = 0.15) after a median follow-up of 40 months, although this did not reach statistical significance (38).

Treatment with gefitinib or erlotinib may also have an impact on the patterns of disease progression and brain failure. Authors have suggested that incomplete drug penetration into the CNS may ultimately permit CNS failure in patients with NSCLC treated with gefitinib or erlotinib (15, 16). Consistent with this hypothesis, published case reports have documented retained sensitivity to high-dose *EGFR*-TKI in patients with *EGFR*-mutated NSCLC who developed leptomeningeal metastases on standard daily dosing of gefitinib or erlotinib (15). Moreover, erlotinib confers higher serum concentrations than gefitinib because of difference of dose setting and might be expected to prevent or delay the onset of CNS involvement. In phase I trials, the mean steady-state plasma concentration attained with 250 mg per day of gefitinib was between 0.16 and 0.24 $\mu\text{g/mL}$, whereas the steady-state trough values measured with erlotinib 150 mg/d ranged from 0.33 to 2.64 $\mu\text{g/mL}$ (39, 40). Our study, however, did not show a difference in the risk of CNS progression based on the drug administered, although this might be due to a small number of patients treated with either gefitinib (*n* = 15) or erlotinib (*n* = 85). Furthermore, it is well recognized that most patients with *EGFR* mutations who initially derive clinical benefit from gefitinib or erlotinib ultimately develop resistance to these drugs and progressive disease. Recent advances have clarified some of the molecular mechanisms that underlay acquired resistance to these agents, including the acquisition of a T790M mutation in exon 20 and the amplification of the *MET* oncogene

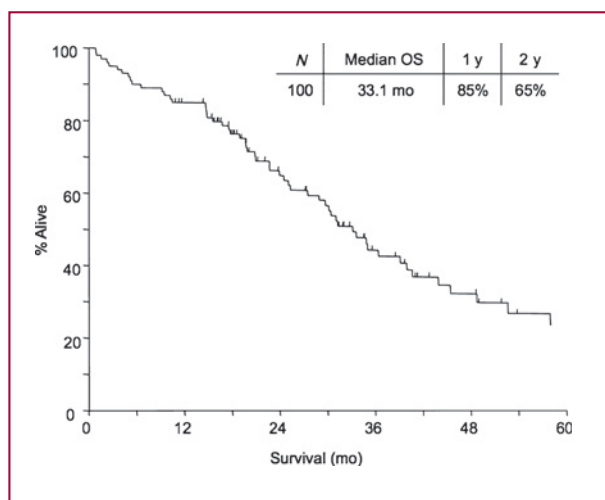


Fig. 3. Kaplan–Meier curve for overall survival (OS) in all eligible patients.

(35, 41). However, few studies have reported on the *EGFR* mutation status in metastatic CNS clones following treatment with gefitinib or erlotinib in patients with *EGFR* mutations. Such comparative molecular analyses are complicated by the limited number of patients who are candidates for resection of BM or who undergo a repeat biopsy when *EGFR*-TKI resistance is encountered. In published autopsy cases, a secondary T790M mutation was found in metastatic sites in 2 patients with *EGFR*-mutated NSCLC who progressed following treatment with gefitinib or erlotinib but was not detected in tumor specimens from the CNS (15, 42). In contrast, 2 patients in our study underwent resection of symptomatic BMs that developed 24 and 37 months after the start of gefitinib therapy. Mutation analysis disclosed a T790M mutation concurrent with an exon 19 deletion in one brain tumor specimen, and an exon 20 insertion mutation, known to confer resistance to *EGFR*-TKI, in the other. Further studies are therefore needed to characterize the molecular evolution of NSCLC and metastatic CNS clones as patients with *EGFR* mutations undergo treatment with gefitinib or erlotinib. This should help elucidate whether these patients develop CNS metastases as a result of inadequate drug exposure behind a relatively intact blood-brain barrier or whether the risk of CNS progression more commonly reflects the selection or acquisition of resistant metastatic clones.

An interesting finding in our study was the difference in the risk of CNS progression between the 2 most common subtypes of *EGFR* mutations. Specifically, tumors bearing exon 19 deletions were associated with a higher 2-year actuarial risk of CNS progression relative to L858R (21% vs. 3%; $P = 0.029$). This difference persisted after multivariate analysis. Notably, median time to progression (16.2 months vs. 11.8 months; $P = 0.026$) and overall survival (40.6 months vs. 23.9 months; $P = 0.014$) were also significantly prolonged in patients with exon 19 deletions compared with *EGFR* L858R. Our data support similar results reported by Jackman et al. (20) and Riely et al. (43), who found that patients with advanced NSCLC and exon 19 deletions had significantly longer median time to progression and overall survival following treatment with gefitinib or erlotinib than patients whose tumor harbored L858R. The survival advantage in favor of exon 19 deletions could have led to a longer period in which these patients could be observed for the development of CNS progression. However, the actuarial risk of CNS progression in our analysis was estimated using the cumulative incidence function in the presence of death as a competing risk, thereby adjusting for a potential difference in death rate between genotypes. Pooling of greater numbers of patients with adequate follow-up and prospective studies are therefore needed to further define the predictive and prognostic roles of different *EGFR* mutations on the outcome of CNS progression following treatment with gefitinib or erlotinib and to explore the biological mechanisms of the differences between the 2 most common types of sensitizing *EGFR* mutations.

Our study also showed that the risk of CNS progression was significantly higher in patients younger than 63 years (hazard ratio, 5.4; $P = 0.003$). Of note, median survival was similar in younger and older patients (34 months vs. 33 months, respectively; $P = 0.517$). The influence of age on the risk of CNS metastases has been observed by others. Ceresoli et al. (17) reported that patients with stage III NSCLC had an increased risk of CNS metastases if they were younger than 60 years (odds ratio, 1.26; $P = 0.03$), whereas Gaspar et al. (44) found that age younger than 50 years predicted for the development of BM following definitive therapy for stage III NSCLC (hazard ratio, 1.8; $P = 0.046$). It remains uncertain why the risk of CNS progression should differ between younger and older patients. One possible explanation is that younger patients and their providers may be more likely to report, detect, and/or investigate changes in neurologic function relative to older patients. Alternatively, the difference in the risk of CNS progression between younger and older patients may be due to a more aggressive course of disease in younger patients. Additional prospective investigations are required to validate these observations.

Our findings are limited to those of any retrospective analysis. Importantly, identification of CNS metastases was usually prompted by new neurologic signs or symptoms, although in some cases, the brain was imaged at the time of systemic disease progression or as part of eligibility screening for a clinical trial. Of the 28 patients with documented CNS progression, 16 patients had symptoms that prompted CNS imaging. The remaining 12 patients were found to have CNS progression in the absence of neurologic symptoms, including 4 patients who underwent imaging of the brain for protocol eligibility. Certainly, more prospective study of this topic with scheduled CNS imaging is warranted. Nevertheless, the inclusion of all patients who met the eligibility criteria at both institutions and the extended follow-up period of 42.2 months should help ensure that the patients studied in this retrospective review are representative of the stage IIIB/IV NSCLC patients with somatic *EGFR* mutations who were treated at both centers during the years of the study. The median time to progression of 13.1 months and overall survival of 33.1 months reported herein also compare favorably with data published in phase III studies of first-line *EGFR*-TKI in molecularly selected patients with advanced NSCLC. In a recent phase III randomized trial conducted by the North-East Japan Study Group, which compared gefitinib or carboplatin plus paclitaxel in previously untreated patients with advanced NSCLC and sensitizing *EGFR* mutations, median progression-free survival and overall survival were 10.8 and 30.5 months, respectively, among patients treated with gefitinib (11). More importantly, the prolonged survival observed in our patients did not coincide with an increased risk for developing CNS metastases. Distinguishing between underlying tumor biology and therapeutic effect of gefitinib or erlotinib on the outcome of CNS progression in patients with advanced NSCLC

harboring *EGFR* mutations and treated with *EGFR*-targeted agents should help provide more effective strategies for chemoprevention and targeted treatment of intracranial and leptomeningeal metastases in this population.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin*. 2009;59:225–49.
- Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol*. 2006;24:4539–44.
- Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008; 26:3543–51.
- Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346:92–8.
- Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007;2:706–14.
- Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced non-small-cell lung cancer: clinical implications for the subsequent management of the brain. *Cancer*. 2007;109:1668–75.
- Mamon HJ, Yeap BY, Janne PA, Reblando J, Shrager S, Jaklitsch MT, et al. High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J Clin Oncol*. 2005;23:1530–7.
- Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947–57.
- Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353:123–32.
- Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med*. 2009;361:958–67.
- Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated *EGFR*. *N Engl J Med*. 2010;362:2380–8.
- Ceresoli GL, Cappuzzo F, Gregorc V, Bartolini S, Crino L, Villa E. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann Oncol*. 2004;15:1042–7.
- Wu C, Li YL, Wang ZM, Li Z, Zhang TX, Wei Z. Gefitinib as palliative therapy for lung adenocarcinoma metastatic to the brain. *Lung Cancer*. 2007;57:359–64.
- Kim JE, Lee DH, Choi Y, Yoon DH, Kim SW, Suh C, et al. Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. *Lung Cancer*. 2009;65:351–4.
- Jackman DM, Holmes AJ, Lindeman N, Wen PY, Kesari S, Borras AM, et al. Response and resistance in a non-small-cell lung cancer patient with an epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib. *J Clin Oncol*. 2006;24:4517–20.
- Omuro AM, Kris MG, Miller VA, Franceschi E, Shah N, Milton DT, et al. High incidence of disease recurrence in the brain and leptomeninges in patients with non-small cell lung carcinoma after response to gefitinib. *Cancer*. 2005;103:2344–8.
- Ceresoli GL, Reni M, Chiesa G, Carretta A, Schipani S, Passoni P, et al. Brain metastases in locally advanced non-small cell lung carcinoma after multimodality treatment: risk factors analysis. *Cancer*. 2002;95:605–12.
- Greene FD, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, et al. , editors. *AJCC Cancer Staging Manual*, 6th edition. New York: Springer-Verlag; 2002.
- Costa DB, Nguyen KS, Cho BC, Sequist LV, Jackman DM, Riely GJ, et al. Effects of erlotinib in *EGFR* mutated non-small cell lung cancers with resistance to gefitinib. *Clin Cancer Res*. 2008;14:7060–7.
- Jackman DM, Yeap BY, Sequist LV, Lindeman N, Holmes AJ, Joshi VA, 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. *Clin Cancer Res*. 2006;12:3908–14.
- Jackman DM, Cioffredi LA, Lindeman N, Morse LK, Lucca J, Weckstein D, et al. Phase II trial of erlotinib in chemotherapy-naïve women with advanced pulmonary adenocarcinoma. *J Clin Oncol*. 2009;27:15s (suppl; abstr 8065).
- Jackman DM, Yeap BY, Lindeman NI, Fidias P, Rabin MS, Temel J, et al. Phase II clinical trial of chemotherapy-naïve patients >or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. *J Clin Oncol*. 2007;25:760–6.
- Janne PA, Gurubhagavatula S, Yeap BY, Lucca J, Ostler P, Skarin AT, et al. Outcomes of patients with advanced non-small cell lung cancer treated with gefitinib (ZD1839, "Iressa") on an expanded access study. *Lung Cancer*. 2004;44:221–30.
- Janne PA, Wang XF, Socinski MA, Crawford J, Capelletti M, Edelman MJ, et al. Randomized phase III trial of erlotinib (E) alone or in combination with carboplatin/paclitaxel (CP) in never or light former smokers with advanced lung adenocarcinoma: CALGB 30406. *J Clin Oncol*. 2010;28(suppl; abstr 7503).
- Sequist LV, Martins RG, Spigel D, Grunberg SM, Spira A, Janne PA, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic *EGFR* mutations. *J Clin Oncol*. 2008; 26: 2442–9.
- Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350:2129–39.
- Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. *EGFR* mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304:1497–500.
- Beasley MB, Brambilla E, Travis WD. The 2004 World Health Organization classification of lung tumors. *Semin Roentgenol*. 2005;40:90–7.
- Chamberlain MC, Glantz M, Groves MD, Wilson WH. Diagnostic tools for neoplastic meningitis: detecting disease, identifying patient risk, and determining benefit of treatment. *Semin Oncol*. 2009;36:S35–45.
- Aalen O. Nonparametric Estimation of Partial Transition Probabilities in Multiple Decrement Models. *The Annals of Statistics*. 1978;6:534–45.

31. Choudhury JB. Non-parametric confidence interval estimation for competing risks analysis: application to contraceptive data. *Stat Med*. 2002;21:1129–44.
32. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *The Annals of Statistics*. 1988;16:1141–54.
33. Jason PF, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999;94:496–509.
34. Sasaki H, Endo K, Takada M, Kawahara M, Kitahara N, Tanaka H, et al. EGFR exon 20 insertion mutation in Japanese lung cancer. *Lung Cancer*. 2007;58:324–8.
35. Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med*. 2005;2:e73.
36. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst*. 2005;97:339–46.
37. Robnett TJ, Machtay M, Stevenson JP, Algazy KM, Hahn SM. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. *J Clin Oncol*. 2001;19:1344–9.
38. Lee YJ, Park IK, Park MS, Choi HJ, Cho BC, Chung KY, et al. Activating mutations within the EGFR kinase domain: a molecular predictor of disease-free survival in resected pulmonary adenocarcinoma. *J Cancer Res Clin Oncol*. 2009;135:1647–54.
39. Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J Clin Oncol*. 2002;20:4292–302.
40. Hidalgo M, Siu LL, Nemunaitis J, Rizzo J, Hammond LA, Takimoto C, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol*. 2001;19:3267–79.
41. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science*. 2007;316:1039–43.
42. Balak MN, Gong Y, Riely GJ, Somwar R, Li AR, Zakowski MF, et al. Novel D761Y and common secondary T790M mutations in epidermal growth factor receptor-mutant lung adenocarcinomas with acquired resistance to kinase inhibitors. *Clin Cancer Res*. 2006;12:6494–501.
43. Riely GJ, Pao W, Pham D, Li AR, Rizvi N, Venkatraman ES, 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. *Clin Cancer Res*. 2006;12:839–44.
44. Gaspar LE, Chansky K, Albain KS, Vallieres E, Rusch V, Crowley JJ, et al. Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol*. 2005;23:2955–61.