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The Impact of Initial Gefitinib or Erlotinib versus Chemotherapy on Central Nervous System Progression in Advanced Non–Small Cell Lung Cancer with *EGFR* Mutations

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Abstract

Purpose: This retrospective study was undertaken to investigate the impact of initial gefitinib or erlotinib (EGFR tyrosine kinase inhibitor, EGFR-TKI) versus chemotherapy on the risk of central nervous system (CNS) progression in advanced non–small cell lung cancer (NSCLC) with *EGFR* mutations.

Experimental Design: Patients with stage IV or relapsed NSCLC with a sensitizing *EGFR* mutation initially treated with gefitinib, erlotinib, or chemotherapy were identified. The cumulative risk of CNS progression was calculated using death as a competing risk.

Results: One hundred and fifty-five patients were eligible (EGFR-TKI: 101, chemotherapy: 54). Twenty-four patients (24%) in the EGFR-TKI group and 12 patients (22%) in the chemotherapy group had brain metastases at the time of diagnosis of advanced NSCLC ($P = 1.000$); 32 of the 36 received CNS therapy before initiating systemic treatment. Thirty-three patients (33%) in the EGFR-TKI group and 26 patients (48%) in the chemotherapy group developed CNS progression after a median follow-up of 25 months. The 6-, 12-, and 24-month cumulative risk of CNS progression was 1%, 6%, and 21% in the EGFR-TKI group compared with corresponding rates of 7%, 19%, and 32% in the chemotherapy group ($P = 0.026$). The HR of CNS progression for upfront EGFR-TKI versus chemotherapy was 0.56 [95% confidence interval (CI), 0.34–0.94].

Conclusions: Our data show lower rates of CNS progression in *EGFR*-mutant advanced NSCLC patients initially treated with an EGFR-TKI compared with upfront chemotherapy. If validated, our results suggest that gefitinib and erlotinib may have a role in the chemoprevention of CNS metastases from NSCLC. *Clin Cancer Res; 1–9. ©2012 AACR.*

Introduction

The development of central nervous system (CNS) metastases is a common and serious complication in non–small cell lung cancer (NSCLC), with an adverse impact on quality of life and survival (1). Phase III trials of cytotoxic chemotherapy for stage IV NSCLC have commonly reported the frequency of brain metastases at the start of systemic therapy, but have seldom differentiated between CNS and non-CNS sites of disease progression during the trial (2, 3). Conversely, the incidence of brain metastases has been widely reported in studies of patients with locally advanced NSCLC treated with definitive locoregional therapies. The addition of chemotherapy to chest irradiation and/or surgical resection in patients with stage III NSCLC has reduced extracranial distant relapses, but has had a limited impact on the frequency of brain metastases, with a 40% to 55% incidence of CNS failure after a median follow-up of 3 years (4, 5). These and other data suggest that conventional chemotherapeutic agents may not cross the intact blood–brain barrier efficiently, leaving the brain relatively at risk for lung cancer relapse, whereas other systemic sites are effectively treated by chemotherapy (6). As systemic therapies for NSCLC continue to improve, prevention and control of brain metastases is likely to emerge as a more vital therapeutic strategy of overall disease control and improved quality of life.

Gefitinib and erlotinib are orally available, reversible inhibitors of the tyrosine kinase domain of the EGF receptor (EGFR) that have shown efficacy in patients with relapsed NSCLC and as initial therapy for patients with advanced NSCLC and sensitizing *EGFR* mutations (7, 8). Prospective trials for patients with previously untreated, *EGFR*-mutant advanced NSCLC have shown response rates of 55% to 75%

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Translational Relevance

Central nervous system (CNS) metastases caused by non–small cell lung cancer (NSCLC) remain a frequent complication, and their occurrence has been altered little by cytotoxic chemotherapy. The EGF receptor (EGFR) tyrosine kinase inhibitors, gefitinib and erlotinib, can penetrate into the CNS and elicit intracranial responses in patients with CNS metastases from NSCLC, but their impact on the outcome of CNS progression remains an area of investigation. Our data suggest that initial treatment of *EGFR*-mutant advanced NSCLC patients with gefitinib or erlotinib significantly lowers the risk of CNS progression during the disease course compared with chemotherapy and hint at the potential of these agents at delaying and/or preventing CNS metastases from NSCLC. As advances in systemic therapy are being made in other genetic subpopulations of NSCLC and other primary tumor types, our observations highlight the importance of studying novel agents in terms of penetration into the CNS.

and progression-free survival of 9 to 13 months for those given gefitinib or erlotinib, approximately 2-fold greater than the results in similar patients treated with chemotherapy (7, 9–11). These results have led to the approval of gefitinib in Europe for patients with sensitizing mutations of *EGFR* in all lines of therapy; erlotinib is recommended as initial treatment for patients with sensitizing *EGFR* mutations in the National Comprehensive Cancer Network guidelines (12, 13).

Evidence from prospective reports has shown that gefitinib and erlotinib can cause regression of established brain metastases from NSCLC, with intracranial response rates reaching 75% in treatment-naive patients with NSCLC with mutated *EGFR* and synchronous brain metastases (14, 15). These data suggest that in a molecularly selected population with brain metastases, gefitinib and erlotinib can achieve high response rates in metastatic brain tumors that have not traditionally been sensitive to conventional chemotherapeutic agents. However, there is incomplete data about the potential impact of EGFR-TKIs on the prevention and control of CNS metastases caused by NSCLC. A CNS-specific pharmacokinetic resistance as a result of poor CSF penetration of gefitinib and erlotinib in the absence of classical genetic mechanisms of acquired resistance to EGFR-TKIs (e.g. *EGFR* T790M) has been described; in published reports, the CSF-to-plasma concentration ratio of either gefitinib or erlotinib was less than 0.01 suggesting that the brain may be a susceptible site for progression of NSCLC targeted by EGFR inhibitors (16, 17). However, our group recently reported on 100 patients with advanced NSCLC and somatic *EGFR* mutations initially treated with gefitinib or erlotinib and found that the risk of developing CNS metastases and/or progression of preexisting brain lesions was approximately 28% after a median potential follow-up of 42 months (18). The 1- and 2-year cumulative risk of CNS progression was 7% and 19%, respectively. These results are substantially less than the published rates of CNS failure in historical series of patients with stage III NSCLC treated with chemotherapy plus chest irradiation and/or surgery as part of a multimodality approach (4, 5). However, the contributing effects of EGFR-targeted therapy and tumor *EGFR* genotype on the risk of CNS progression remain undefined.

Screening for somatic mutations of *EGFR* has been conducted for clinically selected NSCLC patients as part of routine care at our institution since 2004 (19). Therefore, we retrieved information on the clinical presentation and course of our patients with advanced NSCLC and sensitizing *EGFR* mutations, comparing the risk of CNS progression in those initially treated with gefitinib or erlotinib to the risk in similar patients treated with chemotherapy. In particular, we sought to determine whether the apparent decrease in CNS metastases observed in *EGFR*-mutant NSCLC patients treated with an EGFR-TKI was because treatment with gefitinib or erlotinib delays or effectively treats micrometastatic brain disease and, therefore, delays or prevents the development of CNS metastases.

Patients and Methods

Study design and patients

Patients were eligible for this study if they had stage IV NSCLC or stage I–IIIA NSCLC with systemic relapse and sensitizing *EGFR* mutations and were treated with gefitinib, erlotinib, or chemotherapy as their initial systemic therapy for advanced NSCLC (20). Patients who had previously undergone definitive treatment for stage I–IIIA NSCLC that subsequently relapsed were included if surgery with curative intent had been conducted, with or without pre- or postoperative radiation therapy and/or chemotherapy. Neoadjuvant or adjuvant chemotherapy or chemotherapy plus chest radiation therapy was allowed if completed more than 12 months before the start of systemic treatment for relapsed disease. Patients who were started on treatment for advanced NSCLC from August 1, 2000, to June 1, 2010, were included in this analysis to assure 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 (Boston, MA). This patient information has been used for previous reports (18, 21, 22). One hundred and forty-two patients with sensitizing *EGFR* mutations were eligible for inclusion in this study; 73 of these patients have been studied and included in our prior publication on the rates of CNS progression in patients with *EGFR*-mutant advanced NSCLC initially treated with a tyrosine kinase inhibitor of the EGFR (18). One hundred and thirty-two additional patients who were initially treated with chemotherapy for advanced lung adenocarcinoma and who had not previously undergone *EGFR* mutation screening were identified.

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Of the 132 patients, 57 had adequate biopsy specimens available in the Department of Pathology at Brigham and Women's Hospital (Boston, MA) and were referred for *EGFR* sequencing to increase the number of *EGFR*-mutant patients initially treated with chemotherapy. Sensitizing mutations of *EGFR* were shown in 5 of those 57 patients. Therefore, 147 patients from our institution were included in this analysis. Eight additional *EGFR* mutation–positive patients who had met all of the above eligibility criteria were reported by investigators from the Beth Israel Deaconess Medical Center (Boston, MA), a member of the Dana-Farber/Harvard Cancer Center. Seven of these 8 patients have been studied and included in prior publications (18, 21, 23). Thus, 155 patients were included in this analysis, which represent 62% of the 252 patients with somatic mutations of *EGFR* enrolled into both institutions' databases during the years of the study. Ninety-seven patients with *EGFR*-mutant NSCLC were excluded from this analysis because of nonsensitizing *EGFR* mutations (defined later in this section, $n = 21$); early-stage NSCLC without systemic relapse following definitive therapy ($n = 39$); stage III NSCLC treated with definitive chemoradiotherapy ($n = 13$); neoadjuvant or adjuvant chemotherapy completed less than 12 months before the start of systemic therapy for relapsed disease ($n = 5$); advanced NSCLC not treated with systemic therapy ($n = 11$); treatment with erlotinib in the adjuvant setting ($n = 3$); or first-line systemic treatment of advanced NSCLC with chemotherapy plus erlotinib ($n = 4$), or other investigational EGFR-TKI ($n = 1$). The patients included in this report provided written informed consent for the collection of baseline clinical information, analysis of their tumor specimens, and collection of clinical outcomes information.

Mutation analysis

Tumor specimens were analyzed for the presence of somatic mutations of *EGFR* by Sanger dideoxy terminator sequencing of exons 18 to 21 according to previously described methods, with enhanced sensitivity for exon 19 and 21 mutations achieved by the use of specific peptide nucleic acid probes to inhibit amplification of wild-type sequence (24, 25). For those samples ($n = 4$) that were deemed inadequate for conventional sequencing on the basis of review by a molecular pathologist (Neal I. Lindeman) and/or specimens with a low tumor content, SURVEYOR analysis was used as an alternate method of *EGFR* mutation detection, using techniques that have been previously reported (26). For the purposes of this study, the following *EGFR* mutations were considered sensitizing: deletions in exon 19, duplications in exon 19, deletion-insertions of exon 19, L858R point mutation, L861Q point mutation, and G719 missense point mutations (27).

Statistical methods

For all patients, medical records were reviewed to extract data on clinicopathologic characteristics. Tumor histology was classified using the 2004 WHO criteria (28). The distribution of baseline patient characteristics was compared between the treatment groups using Wilcoxon rank-sum test or Fisher exact test.

Data was collected on the prevalence, incidence, and time to development of brain and leptomeningeal metastases from the start of systemic treatment for advanced NSCLC. All patients underwent brain imaging at the time of initial diagnosis of NSCLC and/or at the recognition of advanced disease. Subsequent brain imaging was obtained at the discretion of the treating providers and was generally prompted by symptoms or signs suggestive of CNS involvement. Patients were most frequently evaluated by MRI of the brain, although in some cases, contrast-enhanced computed tomography (CT) was obtained instead of an MRI. CNS metastases included all cases of parenchymal brain metastases and cytologically and/or radiographically diagnosed leptomeningeal disease as previously described (18). Patients classified as having CNS progression included those with newly developed CNS metastases and/or progression of preexisting brain lesions.

Cumulative incidence curves were used to estimate the cumulative risk of CNS progression, and Gray test was used to compare the treatment groups (29). Death without evidence of CNS progression was considered a competing risk in the analysis. If greater than 3 months had elapsed between the date of last clinical follow-up and death without evidence of CNS progression, patients were censored at their time of last clinical follow-up in the analysis of CNS progression. Time to CNS progression and overall survival were estimated using the Kaplan–Meier method, and were calculated from the first day systemic treatment for advanced NSCLC was initiated. The outcome was censored if a patient had not progressed or died at the time of last follow-up. Survival curves were compared by the log-rank test. Competing risks regression based on the proportional subdistribution hazards model was used to estimate the HR for developing CNS progression in the EGFR-TKI versus chemotherapy groups (30). The development of CNS progression was modeled as a time-varying covariate for estimating the associated risk of death by proportional hazards regression. All reported *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).

Results

Patient characteristics

Between August 1, 2000, and June 1, 2010, 155 patients with stage IV or relapsed metastatic NSCLC harboring a sensitizing mutation of *EGFR* were treated with either gefitinib or erlotinib ($n = 101$) or chemotherapy ($n = 54$) as their initial systemic therapy for advanced NSCLC. Our center began routine characterization of *EGFR* in 2004, and has offered protocols of first-line EGFR-TKI therapy for advanced NSCLC since 2002, and for patients with sensitizing *EGFR* mutations since 2005; thus, few *EGFR* mutation–positive advanced NSCLC patients were treated with upfront chemotherapy during the years of the study. Table 1

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Table 1. Baseline patient characteristics

	EGFR-TKI ($N = 101$)	Chemotherapy $N = 54$	P
Age, y			0.38
Median (range)	63 (35–84)	60 (32–85)	
Gender, *n* (%)			0.04
Male	23 (23)	21 (39)	
Female	78 (77)	33 (61)	
Race, *n* (%)			<0.01
White, non-Hispanic	86 (85)	50 (92)	
Asian	12 (12)	0 (0)	
Black	3 (3)	2 (4)	
Hispanic	0 (0)	2 (4)	
Smoking history, *n* (%)			0.05
Never-smoker	58 (57)	20 (37)	
≤10 pack-years	19 (19)	16 (30)	
>10 pack-years	24 (24)	18 (33)	
ECOG PS, *n* (%)[a]			0.34
0–1	95 (94)	46 (85)	
≥2	6 (6)	6 (11)	
Histology, *n* (%)			0.11
Adenocarcinoma	92 (91)	47 (87)	
Squamous	0 (0)	2 (4)	
Large cell carcinoma	0 (0)	1 (2)	
NSCLC NOS	9 (9)	4 (7)	
Stage[b], *n* (%)			0.43
Relapsed[c]	19 (19)	6 (11)	
IVA	34 (34)	18 (33)	
IVB	48 (48)	30 (56)	
Prior BM, *n* (%)	24 (24)	12 (22)	1.00
Prior therapy for BM no.			—
Radiation	21	6	
Resection and radiation	1	4	
None	2	2	
First-line chemotherapy, *n* (%)			—
Platinum doublet	—	49 (91)	
Single agent	—	4 (7)	
Other combination	—	1 (2)	
First-line EGFR-TKI, *n* (%)			—
Gefitinib	11 (11)	—	
Erlotinib	90 (89)	—	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified.

[a]Data not available for 2 patients in the chemotherapy group.

[b]American Joint Committee on Cancer staging system 7th edition.

[c]Patients with stage I-IIIA NSCLC with systemic relapse following definitive therapy that included surgical resection.

shows the demographic and clinical characteristics of the patients according to the initial treatment group. The median age of the study cohort was 61 years (range, 32–85 years) and did not vary significantly by treatment group. There were 44 men and 111 women, and 73% of patients were never or light smokers. Thirty patients included in the EGFR-TKI group were enrolled in prospective trials of first-line erlotinib that selected patients on the basis of clinical features commonly associated with *EGFR* mutations (23, 31). As a result, the proportion of women (77% vs. 61%; $P = 0.04$) and never-smokers (57% vs. 37%; $P = 0.02$) was higher in the EGFR-TKI group compared with the chemotherapy group. Most patients were White, non-Hispanic, although the EGFR-TKI group included a higher percentage of Asian patients (12% vs. 0%; $P < 0.01$). The majority of patients had stage IV disease at the time of

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initial diagnosis of NSCLC (84%) and adenocarcinoma histology (90%). Twenty-five patients had previously undergone definitive treatment for stage I–IIIA NSCLC that subsequently relapsed (16 patients with stage I, 4 with stage II, and 5 with stage IIIA) after a median of 41 months (range, 5–82 months). All patients had undergone resection with curative intent, and 7 of the 25 patients had been treated with neoadjuvant or adjuvant chemotherapy ($n = 5$) and/or radiation therapy ($n = 6$).

Twenty-four patients (24%) in the EGFR-TKI group and 12 patients (22%) in the chemotherapy group had brain metastases at the time of diagnosis of advanced NSCLC, before the initiation of first-line systemic therapy ($P = 1.000$). In the EGFR-TKI group, 20 of the 24 patients were treated with whole brain radiation therapy (WBRT) to doses of 3,000 to 4,050 cGy; 2 of the 20 patients were also treated with stereotactic radiosurgery (SRS) following WBRT. One patient with 3 brain metastases was treated with SRS alone. Another patient underwent resection of a single brain metastasis followed by WBRT. In the chemotherapy group, 6 of 12 patients were treated with WBRT. A single brain metastasis was resected in 3 patients, followed by WBRT in 2 patients or SRS to the surgical cavity in one patient. Another patient with multiple brain metastases underwent resection of a symptomatic cerebellar mass followed by WBRT and SRS to residual lesions. The 4 remaining patients (EGFR-TKI: 2; chemotherapy: 2) had asymptomatic brain metastases measuring 6 mm or less and received no localized CNS therapy before their physicians elected to treat them with erlotinib ($n = 2$) or carboplatin plus paclitaxel ($n = 2$). Notably, 7 of 12 patients (58%) in the chemotherapy group had a single brain metastasis on contrast-enhanced cranial MRI, compared with 3 of 24 patients (13%) in the EGFR-TKI group, explaining, at least in part, the larger proportion of patients who underwent surgical resection followed by postoperative radiation in the chemotherapy group.

EGFR mutation data were available for all patients included in this analysis (Table 2). *EGFR* mutation analysis was

Table 2. *EGFR* gene mutations identified

		Frequency no. (%)[a]	
Exon	**Amino acid change**	**EGFR-TKI**	**Chemo**
18	G719A[b]	2 (2)	2 (4)
	G719C[c]	2 (2)	1 (2)
	G719S	1 (1)	0 (0)
	E709K[d]	1 (1)	0 (0)
19	del[e]	48 (48)	25 (46)
	delins[f]	8 (8)	8 (15)
	K754E[e]	1 (1)	0 (0)
	I740T[f]	1 (1)	0 (0)
	A755D[f]	1 (1)	0 (0)
	D761Y[c]	1 (1)	0 (0)
20	T790M[g]	4 (4)	4 (7)
	S768I[c]	1 (1)	1 (2)
	G779C[b]	1 (1)	0 (0)
21	L858R[d]	34 (34)	18 (33)
	L861Q[b,e,h]	8 (8)	0 (0)
	R776S[e]	1 (1)	0 (0)
	V834L[d]	1 (1)	0 (0)
	G873E[e]	1 (1)	0 (0)
22	M881T[h]	1 (1)	0 (0)

Abbreviations: del, deletion; delins, deletion-insertion.

[a]Twenty-one patients had more than one *EGFR* mutation, including one patient with 3 mutations.

[b]One patient had both G719A and G779C; one patient had both G719A and L861Q.

[c]One patient had both G719C and D761Y; two patients had both G719C and S768I.

[d]One patient had both L858R and E709K; one patient had both L858R and V834L.

[e]One patient had both exon 19 del and K754E; one patient had both exon 19 del and R776S; one patient had all of G873E, L861Q, and exon 19 del.

[f]One patient had both exon 19 delins and I740T; one patient had both an exon 19 delins and A755D.

[g]All 8 patients with T790M had concurrent sensitizing *EGFR* mutations (3 patients with exon 19 del; 2 patients with exon 19 delins; 3 patients with L858R).

[h]One patient had both L861Q and M881T.

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conducted on a pretreatment tissue specimen in 129 patients, whereas a rebiopsy specimen was tested in 15 patients following treatment with an EGFR-TKI. A specimen date was not available in 11 patients. The proportions of classical mutations (deletions or deletion-insertions of exon 19, L858R point mutation) were similar between the 2 groups. All 8 patients with *EGFR* T790M had concurrent sensitizing *EGFR* mutations. Seven of the 8 patients had a clinical response to gefitinib ($n = 2$) or erlotinib ($n = 5$) for a median of 18 months (range, 10–33 months) before showing evidence of progressive disease that harbored both a sensitizing mutation and the resistant T790M mutation on repeat biopsy. Three of the 7 patients had initially been treated with chemotherapy for advanced NSCLC before receiving gefitinib ($n = 1$) or erlotinib ($n = 2$). A pretreatment tissue specimen from these 7 patients was either not available or contained insufficient tumor material for *EGFR* mutation analysis. In these 7 cases, the T790M mutation was presumed secondary and assumed not to be present before an EGFR-TKI was initiated. The remaining patient had *de novo EGFR* T790M without prior exposure to an EGFR-TKI or systemic chemotherapy.

Patterns of disease progression

At the time of this analysis (June 1, 2011), there were 49 patients alive (EGFR-TKI: 36; chemotherapy: 13) with a median follow-up of 30 months (range, 9–97 months). Median follow-up for all eligible patients was 25 months (range, 1–97 months). The follow-up times did not differ significantly between the 2 treatment groups. All but 7 patients had progressive disease or died (EGFR-TKI: 6; chemotherapy: 1). As of the data cutoff point, 18 of the 101 patients in the EGFR-TKI group were continuing to receive their first-line EGFR-TKI (erlotinib in all patients); all patients in the chemotherapy group had discontinued their initial regimen, and 49 of the 54 later received an EGFR-TKI at a median of 6 months (range, 21 days–40 months) from the start of chemotherapy for advanced NSCLC (second-line: 36 patients; third-line: 8 patients; fourth-line: 3 patients; fifth-line: 2 patients). Thirteen of the 36 patients who received second-line treatment with an EGFR-TKI did so before they had radiographic evidence of disease progression, after the identification of a sensitizing mutation of *EGFR*. Five patients were never treated with an EGFR-TKI. Of those 5 patients, 2 died shortly after the identification of a sensitizing *EGFR* mutation, before erlotinib could be initiated; another patient encountered delays in obtaining erlotinib because he was unable to secure second party support (insurance) in a timely fashion for purchase of the drug and passed away; and a sensitizing mutation of *EGFR* was retrospectively identified in 2 patients prompted by this study.

Progression in the CNS occurred in 33 of 101 patients (33%) in the EGFR-TKI group and 26 of 54 patients (48%) in the chemotherapy group. Of the 59 patients who developed CNS progression, 16 had a history of previously treated brain metastases (EGFR-TKI: 9; chemotherapy: 7), whereas 43 did not. Leptomeningeal metastases occurred in 8 patients (8%) in the EGFR-TKI group, and 4 patients (7%) in the chemotherapy group; 8 of these 12 patients had synchronous brain metastases at the time of diagnosis of leptomeningeal involvement. The CNS was the initial site of progression on gefitinib or erlotinib in 8 patients, and the sole site of initial failure in 2 of these 8 patients. The respective numbers for the chemotherapy group were 8 patients as the initial site of progression and 2 as the only site of failure.

The cumulative incidence curves of CNS progression for each group are shown in Fig. 1. The cumulative risk of CNS progression at 6, 12, and 24 months was 1%, 6%, and 21%, respectively, in the EGFR-TKI group, and 7%, 19%, and 32% in the chemotherapy group ($P = 0.026$, Fig. 1A). When the analysis was narrowed to only those 119 patients without preexisting brain metastases, the 6-, 12- and 24-month cumulative rates of CNS progression were 1%, 3%, and 15% in the EGFR-TKI group, compared with corresponding rates of 7%, 17%, and 30% in the chemotherapy group ($P = 0.032$, Fig. 1B). The time to the occurrence of CNS progression from the start of systemic treatment for advanced NSCLC was significantly longer in the EGFR-TKI group than in the chemotherapy group, with a median of 56.0 months versus 31.6 months ($P = 0.010$). The HR of CNS progression for upfront EGFR-TKI versus chemotherapy was 0.56 [95% confidence interval (CI), 0.34–0.94], suggesting a risk reduction of 40%. Because the cohort of patients initially treated with an EGFR-TKI was enriched for women and never-smokers compared with patients treated with upfront chemotherapy, we confirmed that the effect of upfront EGFR-TKI versus chemotherapy retained significance in a multivariate model that adjusted simultaneously for the impacts of gender, smoking history, and prior CNS involvement (adjusted HR, 0.52; 95% CI, 0.32–0.87).

The overall survival did not differ significantly between the 2 treatment groups. The median survival times were 31.0 months for the EGFR-TKI group and 29.8 months for the chemotherapy group ($P = 0.131$; Fig. 2). The development of CNS progression was associated with a 4- to 5-fold increase in the risk of death in both treatment groups ($P < 0.001$). The median survival after the diagnosis of CNS progression was 5.9 and 10.3 months in the EGFR-TKI and chemotherapy groups, respectively ($P = 0.608$).

Discussion

We retrospectively analyzed the impact of initial gefitinib or erlotinib therapy versus chemotherapy on the risk of CNS progression in patients with advanced NSCLC with mutated *EGFR*, and found a significantly lower cumulative risk of CNS progression in patients initially treated with a tyrosine kinase inhibitor of the EGFR compared with chemotherapy. The 6-, 12-, and 24-month cumulative risk of CNS progression was 1%, 6%, and 21% for the EGFR-TKI group compared with 7%, 19%, and 32% for the chemotherapy group ($P = 0.026$), and the cause specific HR for EGFR-TKI versus chemotherapy was 0.56 (95% CI, 0.34–0.94), suggesting a risk reduction of 40%. To our knowledge, this is the first

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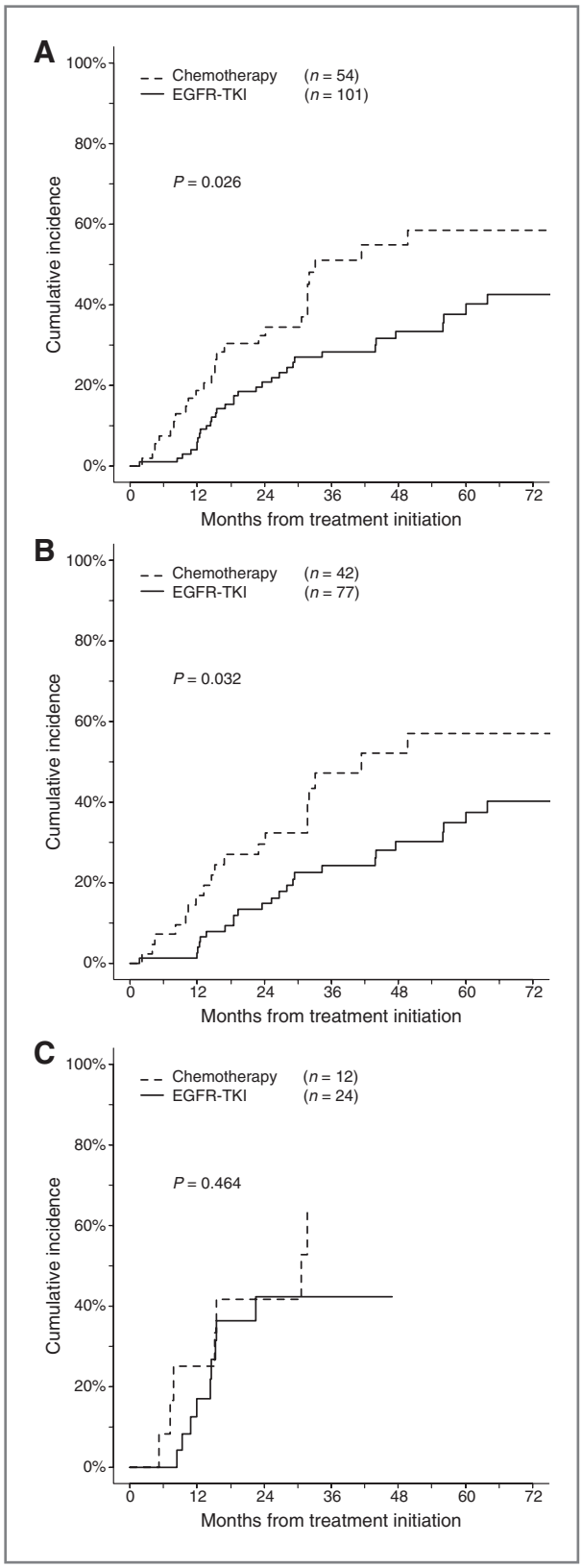

Figure 1. Cumulative incidence of CNS progression in (A) all eligible patients, (B) patients without prior CNS involvement, and (C) patients with prior CNS involvement.

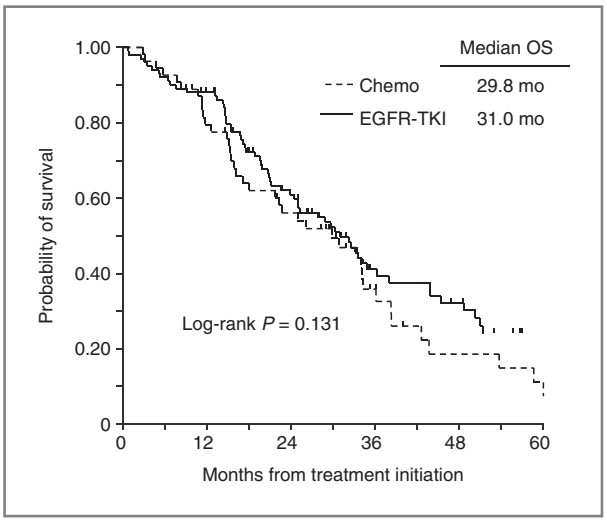

Figure 2. Overall survival in all eligible patients. OS, overall survival.

retrospective study examining the impact of upfront EGFR-targeted therapy versus conventional chemotherapy on the risk of CNS progression in patients with sensitizing *EGFR* mutations, and it offers important insights into the management of this, and potentially other, molecularly defined subset(s) of patients with NSCLC.

The introduction of agents directed against the EGFR has notably expanded the available therapeutic options for patients with advanced NSCLC. In the present study, we extend the data from our prior publication suggesting lower rates of CNS progression (compared with historical estimates) in *EGFR*-mutant advanced NSCLC patients initially treated with gefitinib or erlotinib, and find that the observed lower frequency of CNS metastases seems to be due, at least in part, to the effect of the EGFR-TKI (18). Notably, the lower cumulative rates of CNS progression in the EGFR-TKI group were largely related to a lower risk of CNS metastases in patients without prior CNS involvement ($P = 0.032$) and persisted despite high crossover (91%) to EGFR-targeted therapy in patients initially treated with chemotherapy. The time to the occurrence of CNS progression was also significantly prolonged in the EGFR-TKI group (56.0 vs. 31.6 months, $P = 0.010$), hinting at the potential of gefitinib and erlotinib at slowing the rate of development of CNS metastases from NSCLC. Whether gefitinib and erlotinib can penetrate into the CNS sufficiently to treat micrometastatic CNS disease from NSCLC and thereby prevent the outgrowth of CNS metastases, however, remains uncertain. Previous studies have shown that CNS penetration of erlotinib and gefitinib at standard daily dosing is limited, and authors have suggested that incomplete drug penetration into the CNS may ultimately permit CNS failure in patients with NSCLC treated with gefitinib or erlotinib (17, 32). Investigating the patterns of failure in patients with resected NSCLC and *EGFR* mutations undergoing adjuvant chemotherapy with or without an EGFR-TKI may help elucidate this issue. This approach would allow an evaluation of the limitations of primary therapy, and may help define

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subgroups of patients who perhaps should be treated differently because of a different natural history. Our observations also highlight the importance of elucidating the potential CNS efficacy of novel therapeutic agents. This may be of relevance for designing phase I trials of targeted therapy because the paradigm has been shifting from establishing the maximum tolerated dose to establishing the optimal biologic dose, which may not achieve adequate CNS concentrations (33). The dosing schedule may also be pertinent, for example pulsatile versus continuous (16).

The significance of *EGFR* mutations as a risk factor for CNS progression in NSCLC has not yet been clearly defined. In our study, the risk of CNS progression was not independently examined in a NSCLC cohort without *EGFR* mutations, thereby limiting our ability to evaluate a possible altered biologic predisposition of *EGFR* mutated lung cancer for CNS sites. The significance of *EGFR* mutations on the outcome of CNS progression might be best evaluated in a study with an untreated control arm to distinguish therapeutic effect from underlying tumor biology. One such retrospective surgical series of 117 patients suggested that isolated recurrence in the brain following complete resection of the primary NSCLC was more frequent in patients with tumors bearing an *EGFR* mutation (mutated vs. wild-type *EGFR*, 24% vs. 9%; $P = 0.15$) after a median follow-up of 40 months (34). Given the modest numbers, this did not reach statistical significance. Nonetheless, these data suggest that the lower rates of CNS progression in patients initially treated with an EGFR-TKI in our study might reflect an even more significant alteration in the potential course of disease for patients with *EGFR* mutations.

Our findings are limited to those of any retrospective analysis. First, the observed frequency and patterns of CNS progression were subject to the frequency and thoroughness of clinical and radiographic evaluation. For example, asymptomatic CNS lesions were not specifically sought after, and radiologic confirmation of clinical suspicion was necessary for the identification of CNS progression. However, in the absence of a systematic bias between the 2 treatment groups, our observations should be valid. Similarly, we could not evaluate an interaction between performance status and CNS progression due to the small number of patients with a performance status of 2 or more in both treatment groups (12 of 155, or 8%). Certainly, more prospective study of the topic of CNS progression with scheduled CNS imaging is warranted. Such study could also help define whether surveillance of the brain for early detection of CNS metastases could be useful in patients with *EGFR*-mutant NSCLC.

Our findings also have potentially broader implications, as the armamentarium for personalized therapies expands in lung cancer and other solid malignancies. Anaplastic lymphoma kinase (ALK) is one of the newest molecular targets in NSCLC, and rearrangement of the *ALK* gene defines a subset of NSCLC sensitive to therapeutic ALK inhibition, resulting in significantly improved outcomes for these patients, analogous to those observed for NSCLC patients with *EGFR* mutations treated with an EGFR-TKI (35). Data from an expansion cohort of a phase I trial of the ALK tyrosine kinase inhibitor crizotinib showed 1- and 2-year overall survival rates of 74% and 54%, respectively, in 82 ALK-positive advanced NSCLC patients treated with crizotinib (36). However, a recent case report suggested limited CSF penetration of crizotinib at standard twice daily dosing, with a CSF-to-plasma concentration ratio less than 0.5% and a crizotinib CSF concentration below the concentration required to inhibit growth of cell lines harboring an EML4-ALK translocation by 50% (37). Thus, information will be needed to assess whether the prolonged survival observed in NSCLC patients with ALK translocations treated with crizotinib translates into an increased cumulative risk of CNS progression.

In summary, our results suggest lower rates of CNS progression in *EGFR*-mutant advanced NSCLC patients initially treated with gefitinib or erlotinib compared with upfront chemotherapy. If validated, our findings suggest that gefitinib and erlotinib may be effective at delaying and/or preventing CNS metastases from NSCLC in patients with sensitizing *EGFR* mutations. As new genomically defined subsets of NSCLC are identified that can be targeted with small-molecule inhibitors, such as ALK-rearranged lung cancers responsive to crizotinib, there is a need to conduct carefully designed trials with specific CNS endpoints to evaluate candidates for targeted therapy in terms of CNS penetration, and whether they can treat established CNS metastases and/or prevent them for occurring or recurring.

Disclosure of Potential Conflicts of Interest

V.A. Joshi: employment (KEW Group); ownership interest (KEW Group). D.B. Costa: consultant/advisory board (Pfizer; AstraZeneca; Roche). M.S. Rabin: consultant/advisory board (Genentech). D.M. Jackman: consultant/advisory board (Foundation Medicine; Genentech). B.E. Johnson: ownership interest (KEW Group); consultant/advisory board (Genentech; Pfizer; Chugai; AstraZeneca); post marketing royalties for EGFR mutation testing. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: S. Heon, B.Y. Yeap, N. Lindeman, D.M. Jackman, B.E. Johnson
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Heon, N. Lindeman, V.A. Joshi, M. Butaney, D. B. Costa, M.S. Rabin, D.M. Jackman
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Heon, B.Y. Yeap, N. Lindeman, D.B. Costa, B.E. Johnson
Writing, review, and/or revision of the manuscript: S. Heon, B.Y. Yeap, N. Lindeman, V.A. Joshi, D.B. Costa, M.S. Rabin, D.M. Jackman, B.E. Johnson
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Study supervision: S. Heon, B.E. Johnson

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Stephanie Heon, Beow Y. Yeap, Neal I. Lindeman, et al.

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