

Clinical Experience With Crizotinib in Patients With Advanced *ALK*-Rearranged Non–Small-Cell Lung Cancer and Brain Metastases

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A B S T R A C T

Purpose

Crizotinib is an oral kinase inhibitor approved for the treatment of *ALK*-rearranged non–small-cell lung cancer (NSCLC). The clinical benefits of crizotinib in patients with brain metastases have not been previously studied.

Patients and Methods

Patients with advanced *ALK*-rearranged NSCLC enrolled onto clinical trial PROFILE 1005 or 1007 (randomly assigned to crizotinib) were included in this retrospective analysis. Patients with asymptomatic brain metastases (nontarget or target lesions) were allowed to enroll. Tumor assessments were evaluated every 6 weeks using RECIST (version 1.1).

Results

At baseline, 31% of patients (275 of 888) had asymptomatic brain metastases; 109 had received no prior and 166 had received prior brain radiotherapy as treatment. Among patients with previously untreated asymptomatic brain metastases, the systemic disease control rate (DCR) at 12 weeks was 63% (95% CI, 54% to 72%), the intracranial DCR was 56% (95% CI, 46% to 66%), and the median intracranial time to progression (TTP) was 7 months (95% CI, 6.7 to 16.4). Among patients with previously treated brain metastases, the systemic DCR was 65% (95% CI, 57% to 72%), the intracranial DCR was 62% (95% CI, 54% to 70%), and the median intracranial TTP was 13.2 months (95% CI, 9.9 to not reached). Patients with systemic disease control were also likely to experience intracranial disease control at 12 weeks (correlation coefficient, 0.7652; $P < .001$). Among patients without baseline brain metastases who developed progressive disease ($n = 253$) after initiation of crizotinib, 20% were diagnosed with brain metastases.

Conclusion

Crizotinib was associated with systemic and intracranial disease control in patients with *ALK*-rearranged NSCLC who were *ALK* inhibitor naive and had brain metastases. However, progression of preexisting or development of new intracranial lesions while receiving therapy was a common manifestation of acquired resistance to crizotinib.

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INTRODUCTION

Lung cancer is—and has been for the last several decades—the leading cause of cancer-related mortality for both men and women worldwide.¹ The last decade has revealed the heterogeneity of molecular abnormalities present within non–small-cell lung cancer (NSCLC) and led to the development of tyrosine kinase inhibitors (TKIs), in what is now commonly referred to as precision oncology.^{2,3} Rearrangements, either inversions or translocations,

characterize the genomic changes involving anaplastic lymphoma kinase (*ALK*) that are observed in NSCLC.^{4,5} Inversions in the short arm of chromosome 2 that juxtapose echinoderm microtubule-associated protein-like 4 (*EML4*) with *ALK* and produce *EML4-ALK*–fusion tyrosine kinases^{4,6} are the most common changes noted. The reported prevalence of *ALK* rearrangements in unselected NSCLC is approximately 5%.^{7–12} Tumors with *ALK* rearrangements are addicted to *ALK* signaling and are inhibited by *ALK* TKIs in preclinical models.^{9,13–15}

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Crizotinib—a multitargeted TKI with activity against MET, ALK,¹³⁻¹⁵ and ROS1^{16,17}—was approved by the US Food and Drug Administration in August 2011 for advanced NSCLC positive for ALK rearrangements.^{5,18-20} More recently, the randomized phase III PROFILE 1007 trial showed that for previously treated patients with ALK-rearranged NSCLC, crizotinib led to improved outcomes (progression-free survival [PFS; primary outcome], objective response rate [ORR], and quality-of-life measurements) when compared with docetaxel or pemetrexed.²¹ The median overall survival (OS) of patients with ALK-rearranged NSCLC from the phase I and II trials (PROFILE 1001 and 1005, respectively) was reported as an unprecedented 29.6 months for 120 patients who continued crizotinib even beyond disease progression (PD).²²

Despite the significant clinical experience with crizotinib in controlling systemic sites of tumor burden in patients with ALK-rearranged NSCLC, few reports of any depth have studied whether this ALK inhibitor controls brain metastases in ALK TKI-naïve NSCLC. The CNS is a common site of disease in advanced NSCLC, and patients with CNS metastases are under-represented in clinical trials of systemic therapies.^{18,23,24} As systemic therapies with TKIs continue to improve the duration of disease control for patients with oncogene-driven NSCLCs, the control and prevention of brain metastases have emerged as important therapeutic issues.²⁴ Most systemic cytotoxic chemotherapies and some TKIs seem to inefficiently cross the intact blood–brain barrier.²⁵⁻²⁷ Here, we present a pooled retrospective analysis of crizotinib in patients with ALK-rearranged NSCLC and concurrent brain metastases from the clinical trials PROFILE 1005 and 1007, with the goal of understanding how this TKI affects the control of brain metastases.

PATIENTS AND METHODS

Patients and Treatment

Patients with ALK-rearranged advanced NSCLC enrolled onto PROFILE 1005 or 1007 (randomly assigned to crizotinib) were included in this analysis. These studies are registered with ClinicalTrials.gov as NCT00932451 and NCT00932893, respectively. ALK rearrangement was detected by break-apart fluorescent in situ hybridization.¹⁸ Eligibility criteria for both studies have been described previously²¹ and were similar. Disease was required to be measurable per RECIST (version 1.1)²⁸ for PROFILE 1007. Patients with asymptomatic brain metastases, either treated or untreated at baseline, were eligible for both studies. All patients provided written informed consent, and all patients included in this analysis received crizotinib at a starting dose of 250 mg orally twice per day, with appropriate dosing modification as needed. Data cutoff for this analysis was February 15, 2012, for patients in PROFILE 1005 and March 30, 2012, for those in PROFILE 1007. Our study was a retrospective exploratory analysis of PROFILE 1005 and 1007.

Measurements of Systemic Disease and Brain Sites of Disease

Tumor assessments were performed every 6 weeks from the date of first dose (PROFILE 1005) or the date of random assignment (PROFILE 1007), and all analyses were based on investigator assessment using RECIST (version 1.1). Baseline brain imaging was required in both studies, and if brain metastases were detected (investigators used either computed tomography only [$n = 134$], magnetic resonance imaging only [$n = 138$], or both modalities [$n = 1$] for patients with detected brain metastases; for two patients, neither method of imaging was recorded), subsequent brain imaging was required at 6-week intervals. Otherwise, imaging to assess brain metastases on treatment was performed as clinically indicated. Systemic lesions and brain metastases were monitored as target or nontarget lesions.

Statistical Analyses

Because a majority of baseline brain metastases in these two studies were identified as nontarget lesions, disease control rate (DCR) at 12 weeks (to allow at least two imaging reassessments) was determined to be the best clinical correlate of intracranial benefit using RECIST (version 1.1) for this retrospective analysis. DCR (systemic [ie, all sites outside brain] or intracranial) was defined as the percentage of patients with complete response (CR), partial response (PR), or stable disease. Both intracranial and systemic DCRs were evaluated at 12 weeks after the start of treatment or random assignment. Best overall objective response for measurable intracranial lesions was also determined. A confirmatory imaging assessment was required to confirm CR or PR. Systemic time to progression (TTP) was defined as the time from the first dose (PROFILE 1005) or from random assignment (PROFILE 1007) to the first documentation of objective systemic tumor progression. Intracranial TTP was defined as the time from the first dose (PROFILE 1005) or from random assignment (PROFILE 1007) to the first documentation of intracranial tumor progression.

PFS, TTP, and OS were analyzed using the Kaplan-Meier method. The median event time and the corresponding two-sided 95% CI (Brookmeyer–Crowley method) were provided. Systemic and intracranial DCRs at 12 weeks were analyzed for degree of association using Pearson's χ^2 test, and the ϕ coefficient was provided. Differences between baseline clinicopathologic characteristics of the groups were assessed using Pearson's χ^2 or Fisher's exact test and indicated accordingly. All analyses were performed with SAS statistical software (version 9.2; SAS Institute, Cary, NC). Additional details can be found in the Appendix (online only).

RESULTS

Baseline Characteristics of Patients

Baseline clinicopathologic characteristics of the 888 patients pooled from PROFILE 1005 and 1007 are listed in Table 1. Three groups within this pooled population were defined (Fig 1): one, patients with untreated (no prior radiotherapy) asymptomatic brain metastases (12%); two, patients with previously treated (with intracranial radiotherapy at any time during cancer course) asymptomatic brain metastases (19%); and three, patients with no detectable brain metastases at baseline (69%). The three groups were similar with regard to most baseline characteristics, except age and ethnicity (more Asians in untreated brain metastases group, which may reflect local clinical practices in management of CNS disease rather than tumor biology) and the duration of crizotinib treatment (median, 24.7 [range, 0.1 to 81.7], 22.0 [1.4 to 102.4], and 29.3 weeks [0.3 to 108.3], respectively). Treatment-emergent adverse events were similar for patients with or without baseline brain metastases while receiving crizotinib (data not shown).

Disease Control With Crizotinib

All 888 patients included in the analysis were evaluable for systemic response (Table 2). In the patients with untreated brain metastases, the systemic DCR at 12 weeks was 63% (95% CI, 54% to 72%). These same patients had an intracranial DCR of 56% (95% CI, 46% to 66%) at 12 weeks. Systemic ORR in this group of patients was 53% (95% CI, 43% to 63%). The intracranial ORR, which only accounts for confirmed CRs and PRs of target CNS lesions, was 18% (95% CI, 5% to 40%) in the group with target baseline lesions (Table 2).

In patients with previously treated brain metastases, the systemic DCR at 12 weeks was 65% (95% CI, 57% to 72%). These patients had an intracranial DCR of 62% (95% CI, 54% to 70%) at 12 weeks.

Table 1. Clinicopathologic Characteristics of Patients With and Without BM at Baseline

Characteristic	Previously Untreated Asymptomatic Baseline BM (n = 109)		Previously Treated Asymptomatic Baseline BM (n = 166)		No Detected Baseline BM (n = 613)		P
	No.	%	No.	%	No.	%	
Age, years							
Median	48		48		54		—
Range	22-77		19-81		24-83		—
Age distribution, years							.0307*
< 65	96	88	150	90	507	83	
≥ 65	13	12	16	10	106	17	
Sex							.9571*
Male	46	42	73	44	264	43	
Female	63	58	93	56	349	57	
Ethnicity							< .001*
Asian	76	70	90	54	231	38	
White	31	28	71	43	356	58	
Other	2	2	5	3	26	4	
Smoking status							.6398*
Never	70	64	107	64	408	67	
Former	32	29	53	32	184	30	
Current	7	6	6	4	21	3	
Tumor histologic type							.3385†
Adenocarcinoma	105	96	159	96	572	93	
Nonadenocarcinoma	4	4	7	4	41	7	
ECOG PS							.6051*
0	21	19	40	24	186	30	
1	68	62	96	58	332	54	
2	16	15	23	14	81	13	
3	4	4	7	4	14	2	
Extent of disease							.2903*
Locally advanced	6	6	8	5	49	8	
Metastatic	103	94	158	95	564	92	
BM lesion type							.0840*
Target only	9	8	9	5	NA		
Target and nontarget	13	12	9	5	NA		
Nontarget	87	80	148	89	NA		

Abbreviations: BM, brain metastases; ECOG, Eastern Cooperative Oncology Group; NA, not applicable; PS, performance status.

*Pearson's χ^2 test; for ethnicity, Asian was compared with non-Asian; for ECOG PS, 0 to 1 was compared with 2 to 3.

†Fisher's exact test.

Systemic and intracranial (within aforementioned limitations) ORRs in this group were 46% (95% CI, 39% to 54%) and 33% (95% CI, 13% to 59%), respectively, in the group with target lesions.

When systemic DCR at 12 weeks was evaluated in conjunction with intracranial DCR at 12 weeks, a positive and statistically significant relationship was found (correlation coefficient, 0.7652; $P < .001$) in the pooled group of patients with previously treated or untreated brain metastases, suggesting that patients with systemic DCR at 12 weeks were also likely to experience intracranial DCR at 12 weeks and vice versa.

In patients with target CNS lesions with previously untreated (Fig 2A) and treated (Fig 2B) brain metastases, target lesion tumor regression was observed even when not confirmed as an objective response. This observation was noted in the majority of patient cases. In patients with no detectable brain metastases at baseline, the systemic DCR at 12 weeks was 71% (438 of 613), and the systemic ORR was 55% (336 of 613).

Disease Control and Sites of PD With Crizotinib

Overall and median PFS for patients with or without brain metastases from the initiation of crizotinib treatment are depicted in Figure 3A and Table 2, respectively. The systemic PFS (Table 2; Fig 3B) was similar for patients with or without brain metastases before initiation of crizotinib.

For patients with untreated brain metastases, the median intracranial TTP was 7 months (95% CI, 6.7 to 16.4), and the median systemic TTP was 12.5 months (95% CI, 7.0 to 14.0), as shown in Figure 4A and Table 2. Progression during crizotinib treatment occurred in 43% of patients (47 of 109) in this group at the time of data cutoff. Of the patients with nontarget or new lesions as PD, the CNS was the most common site of progression, occurring in 70% of patients (30 of 43).

For patients with previously treated brain metastases, the median intracranial TTP was 13.2 months (95% CI, 9.9 to not reached), and the systemic median TTP was 14 months (95% CI, 13.5 to 18.0), as

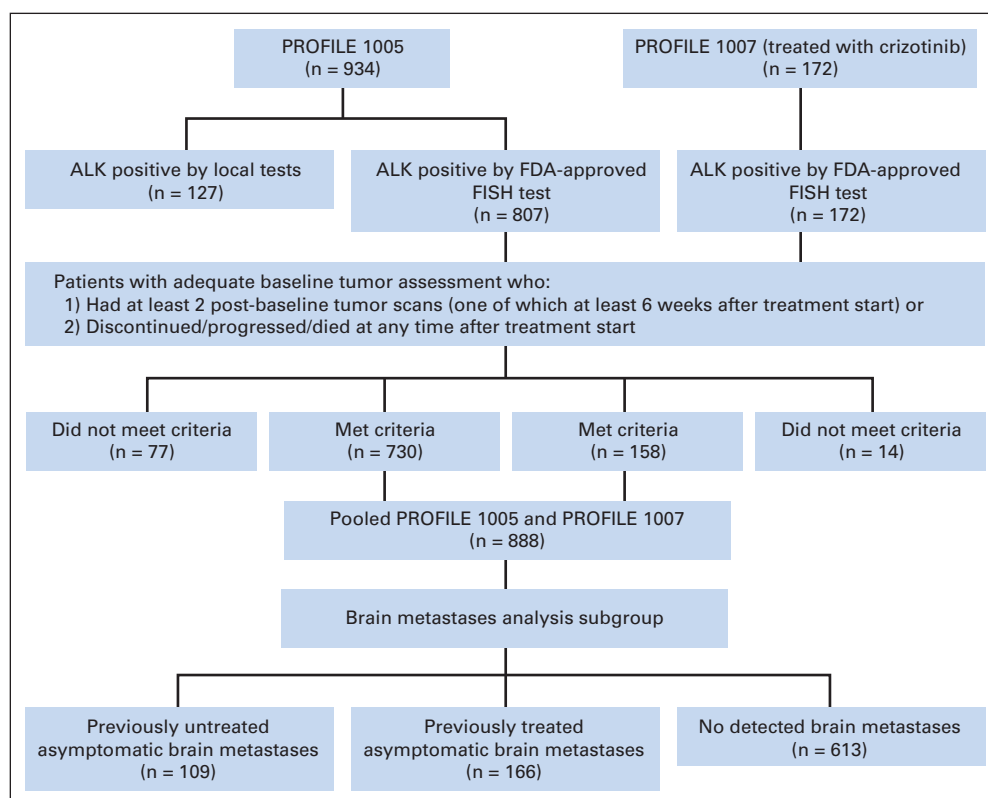


Fig 1. CONSORT diagram. ALK, anaplastic lymphoma kinase; FDA, US Food and Drug Administration; FISH, fluorescent in situ hybridization.

shown in Figure 4B and Table 2. Progression while receiving crizotinib occurred in 37% of patients (62 of 166) at the time of data cutoff. Of the patients with nontarget or new lesions as PD, the CNS was the most common site of progression, occurring in 72% of patients (39 of 54).

For patients without evidence of brain metastases at initiation of crizotinib treatment, the median overall TTP was 9.8 months (95% CI, 8.4 to 11.7). The development of brain metastases (by investigator review of imaging scans) occurred in 20% of patients (51 of 253) with PD at the time of data cutoff. The median time to detection of brain metastases in these 51 patients was 29.9 weeks (range, 2.6 to 79 weeks).

In all patients, including those with progressive brain metastases, continued use of crizotinib was allowed if the treating physician believed the patient continued to derive clinical benefit. Data from 34 patients with new brain metastases (from group without initially detected brain metastases) in whom this approach was undertaken were evaluated. In this group of patients, the post-PD median treatment duration was 19.3 weeks (range, 3.1 to 63.6 weeks). Of these, most (27 of 34) received local CNS treatment (with whole-brain radiotherapy or stereotactic radiotherapy) followed by continued crizotinib, whereas seven patients continued crizotinib beyond PD and did not receive radiotherapy.

OS During Crizotinib Treatment

OS was immature by the data cutoff date for this analysis, with only 29%, 34%, and 27% of patients known to have died in the groups with untreated brain metastases, previously treated brain metastases, and no detectable brain metastases at baseline, respectively. Preliminary estimates for the 6-month survival probabilities were 77% (95% CI, 67% to 85%), 74% (95% CI, 66% to 80%), and

85% (95% CI, 81% to 87%) for the three groups with untreated, previously treated, and no brain metastases, respectively; preliminary estimates for the 1-year survival probabilities were 59% (95% CI, 45% to 70%), 64% (95% CI, 55% to 71%), and 69% (95% CI, 64% to 73%) for these three groups, respectively.

DISCUSSION

Crizotinib is a multitargeted TKI with proven efficacy against *ALK*-rearranged tumors and is approved in several countries for the treatment of *ALK*-rearranged advanced NSCLC.^{18,29} Approximately one third of patients with advanced *ALK*-rearranged NSCLC after failure of at least one prior systemic therapy, as described here, have brain metastases at baseline. The penetration of crizotinib into the CNS and measurements of CSF concentrations of the drug have not been fully investigated. Most small-molecule TKIs—including crizotinib,³⁰ imatinib,²⁵ erlotinib,²⁶ and gefitinib²⁷—have been shown to have low CSF-to-plasma ratios. However, it was unclear before our analysis whether crizotinib had activity in the management of brain metastases.

To our knowledge, our retrospective analysis of crizotinib-treated patients with *ALK*-rearranged NSCLC and asymptomatic treated or untreated brain metastases pooled from PROFILE 1005 and 1007 represents the largest data set on brain metastases in *ALK*-rearranged NSCLC analyzed to date. It demonstrated a high degree of concordance between initial disease control of brain metastases and systemic sites of malignancy. A majority of patients with brain metastases did not have systemic or CNS progression within the first 12 weeks of crizotinib therapy. The main limitations of these data are that

Table 2. Crizotinib Antitumor Activity in Patients With and Without BM at Baseline

Activity	Previously Untreated for BM (n = 109)			Previously Treated for BM (n = 166)			No BM Detected (n = 613)		
	No. of Patients	Outcome	95% CI	No. of Patients	Outcome	95% CI	No. of Patients	Outcome	95% CI
DCR at 12 weeks, %									
IC	109	56	46 to 66	166	62	54 to 70		NA	
Systemic	109	63	54 to 72	166	65	57 to 72	613	71	68 to 75
ORR, %									
IC (target lesion BM)	22	18	5 to 40	18	33	13 to 59		NA	
Systemic	109	53	43 to 63	166	46	39 to 54	613	55	51 to 59
Time to tumor response, weeks									
IC	8			12					
Median		6.0			6.4			NA	
Range*		4.9-12.4			5.9-17.7			NA	
Systemic	58			77			336		
Median		6.1			6.1			6.1	
Range*		2.0-31.4			3.1-35.3			3.0-49.1	
Duration of response, weeks									
IC	8			12					
Median†		26.4			NR			NA	
Range*		6.1-59.3			6.0-59.9			NA	
Systemic	58			77			336		
Median†		47.9			55.6			49.0	
Range*		5.3-55.0			4.4-95.3			4.1-96.1	
Median PFS, monthst									
Overall	109	5.9	4.2 to 6.9	166	6.0	4.3 to 9.9	613	8.8	7.9 to 9.9
Systemic	109	8.3	6.7 to 14.0	166	13.5	6.2 to 16.5	613	9.9	8.8 to 12.2
Median TTP, monthst									
IC	109	7.0	6.7 to 16.4	166	13.2	9.9 to NR		NA	
Systemic	109	12.5	7.0 to 14.0	166	14.0	13.5 to 18.0		NA	

Abbreviations: BM, brain metastases; DCR, disease control rate; IC, intracranial; NA, not applicable; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TTP, time to progression.

*In patients with respective type of objective response.

†Kaplan-Meier method.

CNS lesions were measured using RECIST, and most of these lesions were identified as nontarget lesions at baseline; in addition, the radiotherapy schemes to palliate brain metastases were not specified or standardized in the PROFILE 1005 and 1007 clinical trials. The late effects of radiotherapy on subsequent intracranial response to TKIs are unknown. Notwithstanding, the presence of confirmed intracranial responses (with measurable decrease in target lesions), as detailed here, can be taken to provide evidence of CNS activity from crizotinib

in *ALK*-rearranged *ALK* TKI-naïve patients. Case reports of CNS responses to crizotinib in crizotinib-naïve patients have also been described by others.³¹ However, progression of pre-existing or development of new intracranial lesions while receiving crizotinib therapy was common. Median TTPs were numerically lower for intracranial than for systemic baseline disease. In patients without brain metastases at the time of initiation of crizotinib treatment, 20% of those who subsequently experienced progression had the CNS as a site of disease

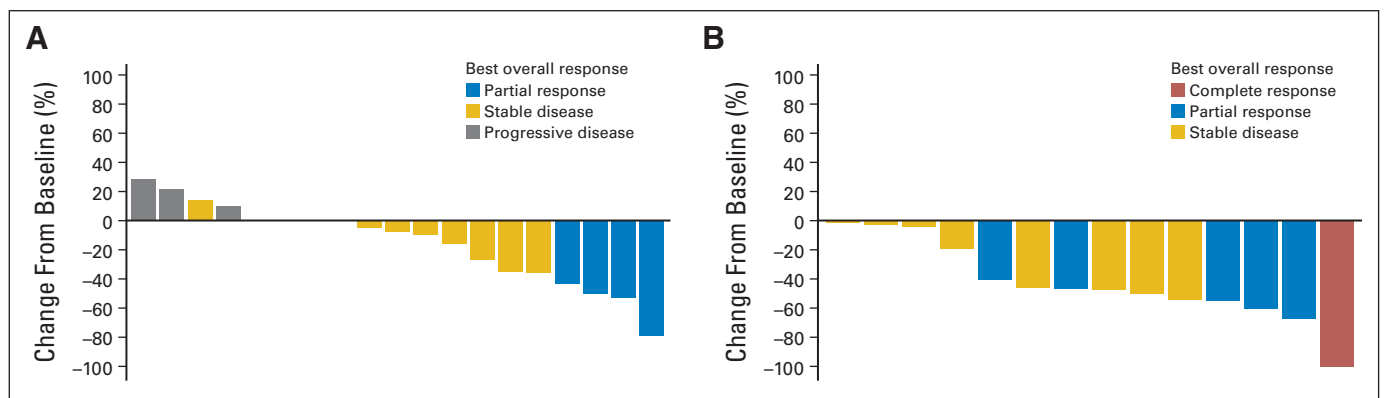


Fig 2. Waterfall plots of best percentage change in intracranial target lesions for patients with \geq one intracranial target lesion at baseline with previously (A) untreated or (B) treated brain metastases.

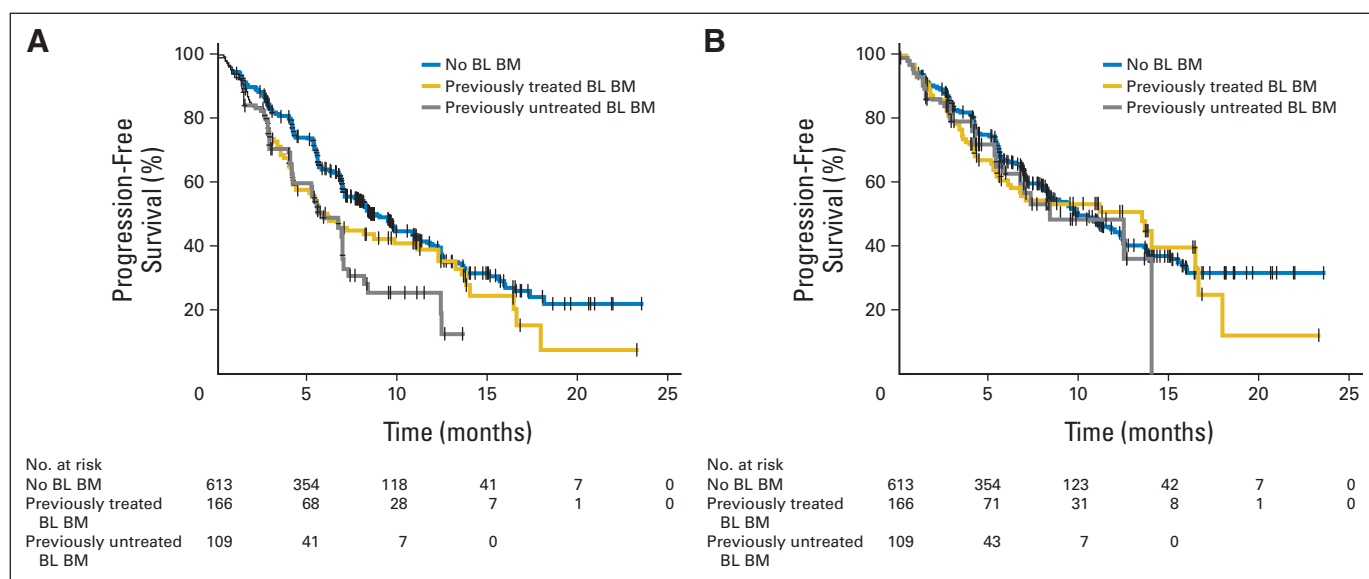


Fig 3. (A) Overall and (B) systemic progression-free survival by treatment group. BL, baseline; BM, brain metastases.

progression. In patients with known brain metastases, the CNS was a site of new lesion or nontarget PD in 70% of patient cases of PD during crizotinib treatment. These latter numbers are not dissimilar from data available for other oncogene-driven NSCLCs treated with TKIs, such as epidermal growth factor receptor (*EGFR*)–mutated NSCLC treated with gefitinib or erlotinib.^{32,33} In one report of *EGFR*-mutated NSCLC, the cumulative incidence of brain metastases in patients without such metastases detected before initiation of *EGFR* TKI treatment hovered at approximately 15% after a median of 2 years of follow-up, and progression of previously known brain metastases was almost 50% after initiation of gefitinib or erlotinib.^{23,24} It is possible that other oncogene-driven lung tumors treated with TKIs will have similar patterns of CNS progression.

Of note, the natural history of *ALK*-rearranged NSCLC within the CNS and its expected rate of progression over time are poorly understood. A direct comparison between how pemetrexed-platinum

chemotherapy and crizotinib affect the rate of CNS disease control and the occurrence of the CNS as a primary site of PD is planned for the ongoing first-line PROFILE 1014 randomized trial (ClinicalTrials.gov identifier NCT01154140); this may provide additional insight into how crizotinib may affect the natural history of CNS disease in *ALK*-rearranged NSCLC. CNS activity has been reported with other multitargeted *ALK* TKIs, such as ceritinib^{12,34} and alectinib,^{35,36} in patients with *ALK*-rearranged NSCLC who are naive or resistant to crizotinib therapy. Direct comparisons among the *ALK* TKIs in their systemic and intracranial activities are ongoing. Acquired resistance¹² to crizotinib and the other *ALK* TKIs in patients with *ALK*-rearranged NSCLC remains the main limitation in the prolonged palliative benefit of this class of compounds. Acquired resistance to TKI therapy is a common thread among many oncogene-addicted NSCLCs.³⁷ In the case of *ALK*-rearranged NSCLC, the major mechanisms of systemic acquired resistance include *ALK* tyrosine kinase mutations, *ALK* copy

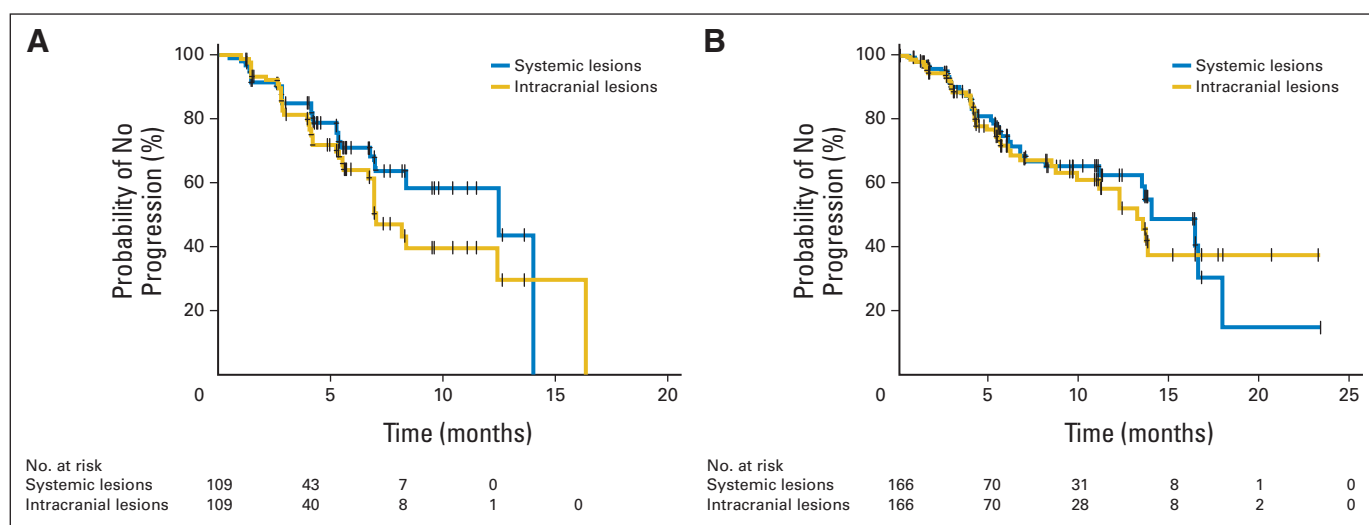


Fig 4. Systemic and intracranial time to progression in patients with previously (A) untreated and (B) treated brain metastases.

number gains, and oncogene activation of bypass pathways¹²; however, the main mechanisms explaining CNS progression and parenchymal brain concentrations of ALK TKIs are unknown.

The management of isolated sites of progression is not an uncommon clinical presentation among patients treated with crizotinib in the setting of acquired resistance. As reported here, the CNS is often a site of progression. In such cases, many oncologists have instituted policies providing local therapy options (such as whole-brain radiotherapy or stereotactic brain radiotherapy) while continuing crizotinib for systemic disease control, a strategy that seems to provide clinical benefit and prolong the time that crizotinib can provide systemic disease control of nonprogressing lesions.^{20,22,38} Among patients with PD in PROFILE 1001 and 1005, the cohort that continued to receive crizotinib despite RECIST-determined progression (62% of 194 patients with PD) had significantly longer OS (both from time of PD and from initial crizotinib treatment) than the group that did not continue crizotinib beyond progression.²² Newer strategies to manage CNS progression are eagerly awaited for ALK-rearranged NSCLC with intracranial sites of PD. A novel multitargeted ALK and ROS1 TKI—PF-06463922 (low-efflux substrate of P-glycoprotein)—was designed to increase potential CNS penetration and to act as a more potent ALK TKI than crizotinib.³⁹ A phase I clinical trial of PF-06463922 (ClinicalTrials.gov identifier NCT01970865) is under way and may demonstrate whether this drug can be effective in treating patients with ALK-rearranged NSCLC with CNS disease in the crizotinib-naïve or -resistant setting.

In summary, we report, to our knowledge, the largest cohort of patients with ALK-rearranged NSCLC with brain metastases. Crizotinib was associated with more than 55% disease control within the CNS at 12 weeks of therapy, comparable to the rate observed system-

ically. Crizotinib was also associated with a moderate (18% to 33%) but RECIST-confirmed CNS ORR among patients with measurable brain metastases before initiation of this TKI. However, the CNS remains one of the dominant sites of progressive tumor burden during crizotinib therapy. Further research into mechanisms of acquired progression within the CNS during therapy with crizotinib and other ALK TKIs will help define the use of these agents in this setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors

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GLOSSARY TERMS

anaplastic lymphoma kinase (ALK): an enzyme that, in humans, is encoded by the *ALK* gene.

non-small-cell lung cancer (NSCLC): a type of lung cancer that includes squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.

tyrosine kinase inhibitors: molecules that inhibit the activity of tyrosine kinase receptors. Tyrosine kinase inhibitors are small molecules developed to inhibit the binding of ATP to the cytoplasmic region of the receptor (eg, gefitinib), thus further blocking the cascade of reactions that is activated by the pathway.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Clinical Experience With Crizotinib in Patients With Advanced *ALK*-Rearranged Non–Small-Cell Lung Cancer and Brain Metastases

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Appendix

Crizotinib and Clinical Trials

Crizotinib has been evaluated in *ALK*-rearranged non-small-cell lung cancer (NSCLC) in the following clinical studies: the expansion cohort of a phase I trial (PROFILE 1001; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00585195) identifier NCT00585195), a phase II trial (PROFILE 1005; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00932451) identifier NCT00932451), and two worldwide phase III trials (PROFILE 1007; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00932893) identifier NCT00932893 [crizotinib v chemotherapy in second-line setting] and PROFILE 1014; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01154140) identifier NCT01154140 [crizotinib v chemotherapy in first-line setting]). In the initial 149 patients with *ALK*-rearranged NSCLC from the PROFILE 1001 trial, crizotinib led to a response rate (RR) of 60.8% (95% CI, 52.3 to 68.9), with a median progression-free survival (PFS) of 9.7 months (95% CI, 7.7 to 12.8) and an estimated overall survival (OS) of 74.8% (95% CI, 66.4 to 81.5) at 12 months.^{18,19} The results of PROFILE 1005 have not been published. In PROFILE 1007, crizotinib was associated with an RR of 65% (95% CI, 58 to 72), as compared with an RR of 20% (95% CI, 14 to 26) with chemotherapy (docetaxel or pemetrexed); the median PFS also was improved with crizotinib to 7.7 months, as compared with 3.0 months in the chemotherapy group (hazard ratio for progression or death with crizotinib, 0.49; 95% CI, 0.37 to 0.64; $P < .001$); the median OS was 20.3 months (95% CI, 18.1 to not reached) with crizotinib and 22.8 months (95% CI, 18.6 to not reached) with chemotherapy (hazard ratio for death in crizotinib group, 1.02; 95% CI, 0.68 to 1.54; $P = .54$).²¹

Patients and Treatment

Key differences between PROFILE 1005 and 1007 were that patients enrolled onto PROFILE 1007 could only have had one prior chemotherapy regimen that had to have been platinum based, whereas those in PROFILE 1005 could have had more than one prior regimen, with non-platinum-based regimens allowed.

Measurements of Systemic Disease and Brain Sites of Disease

Per RECIST (version 1.1), lesions situated in previously irradiated areas are not considered measurable unless they demonstrate progression after irradiation. The late effects of prior radiotherapy on measurements of lesions using RECIST (version 1.1) are unknown for *ALK*-rearranged NSCLC. Target lesions (which generally include all measurable lesions representative of all involved organs) were measured at baseline and at each stipulated imaging assessment. All other lesions, considered nontarget lesions, were observed at baseline and on treatment but were assessed only qualitatively to be present, absent, or increased (represented unequivocal progression). In contrast to RECIST categories defined for target lesions (complete response, partial response, stable disease, and progressive disease [PD]), response in nontarget lesions was defined only as complete response (disappearance of all nontarget lesions), stable disease (persistence of \geq one nontarget lesion), and PD (unequivocal progression of existing nontarget lesions or appearance of \geq one new lesion). In the absence of standard minimum tumor growth criteria defining individual sites of PD when there were multiple sites of progressing target lesions, we analyzed the subset of patients who had PD involving new lesions and/or nontarget lesions.

Statistical Analyses

The 6-month survival probability was estimated using the Kaplan-Meier method, and a two-sided 95% CI for the log [$-\log(6\text{-month survival probability})$] was calculated using a normal approximation and then back transformed to give a CI for the 6-months survival probability itself. The 1-year survival probability was estimated similarly.

Overall PFS was defined as the time from the first dose (PROFILE 1005) or from random assignment (PROFILE 1007) to the first documentation of objective tumor progression or death resulting from any cause (whichever occurred first). Systemic PFS was defined similar to overall PFS, but only sites of systemic (extracranial) disease were evaluated for tumor progression. OS was defined as the time from the first dose (PROFILE 1005) or from random assignment (PROFILE 1007) to the date of death resulting from any cause. Duration of follow-up for overall PFS was calculated based on the reverse Kaplan-Meier method. The median duration of follow-up for overall PFS for patients with untreated brain metastases was 5.9 months, for patients with previously treated brain metastases, 8.2 months, and for patients without brain metastases, 9.5 months.