FAST TRACK

Alectinib Salvages CNS Relapses in ALK-Positive Lung Cancer Patients Previously Treated with Crizotinib and Ceritinib

Justin F. Gainor, MD, Carol A. Sherman, MD,† Kathryn Willoughby, MD,† Jennifer Logan, NP, MS,* Elizabeth Kennedy,* Priscilla K. Brastianos, MD,*‡ Andrew S. Chi, MD, PhD,‡ and Alice T. Shaw, MD, PhD**

Background: Leptomeningeal metastases (LM) are an increasingly frequent and devastating complication of anaplastic lymphoma kinase (*ALK*)-rearranged non–small-cell lung cancer (NSCLC). Currently, the optimal management of LM in ALK-positive patients remains poorly understood as these patients have been routinely excluded from clinical trials.

Methods: We describe four ALK-positive patients with LM who were treated with the next-generation ALK inhibitor alectinib through single-patient, compassionate use protocols at two institutions. All patients had previously been treated with both FDA-approved ALK inhibitors—crizotinib and ceritinib. Patients received alectinib at a starting dose of 600 mg twice daily.

Results: Four ALK-positive NSCLC patients with symptomatic leptomeningeal disease were identified. Three of four patients experienced significant clinical and radiographic improvements in LM upon treatment with alectinib. A fourth patient had stable intracranial disease for 4 months before eventual systemic disease progression. Overall, alectinib was well tolerated. One patient required dose reduction due to grade 2 hyperbilirubinemia.

Conclusions: Alectinib is active in *ALK*-rearranged NSCLC patients with LM, including in patients previously treated with crizotinib and ceritinib. Additional prospective studies of alectinib in ALK-positive patients with LM are warranted.

Key Words: ALK, Anaplastic lymphoma kinase, Leptomeningeal metastases, Alectinib.

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*Department of Medicine, Massachusetts General Hospital, Boston, MA; †Department of Medicine, Medical University of South Carolina, Charleston, SC; and ‡Department of Neurology, Massachusetts General Hospital, Boston, MA.

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Address for Correspondence: Alice T. Shaw, MD, PhD, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114. E-mail: ashaw1@partners.org

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Anaplastic lymphoma kinase (*ALK*) rearrangements are important therapeutic targets in non–small-cell lung cancer (NSCLC) that confer sensitivity to ALK tyrosine kinase inhibitors (TKIs).[1,2] Crizotinib was the first ALK tyrosine kinase inhibitor approved for ALK-positive NSCLC based upon randomized studies demonstrating significant improvements in objective response rates and progression-free survival compared with cytotoxic chemotherapy.[3] Despite this activity, however, patients ultimately progress on therapy, at which time management approaches commonly include treatment with second-generation ALK inhibitors (e.g., ceritinib, AP26113, and alectinib) or chemotherapy.

Recently, the central nervous system (CNS) has emerged as an important sanctuary site in ALK-positive NSCLC. Approximately 26% of ALK-positive patients with newly diagnosed, metastatic disease have CNS metastases.[4] The incidence of CNS metastases also appears to increase with disease course. For example, among crizotinib-treated patients enrolled on trials of second-generation ALK inhibitors, rates of CNS metastases have been as high as 60%.[5] ALK-positive patients may also experience less common forms of CNS involvement, such as spinal cord intramedullary and leptomeningeal metastases (LM).[6,7]

Herein, we present a series of four ALK-positive NSCLC patients who developed LM on or after treatment with crizotinib and ceritinib, and were treated with the second-generation ALK inhibitor alectinib (CH5424802/RO5424802). Alectinib is a novel, highly potent and selective ALK inhibitor that has demonstrated promising antitumor activity in early phase trials.[8]

PATIENTS AND METHODS

Patients were treated with alectinib through single-patient, compassionate use protocols at two institutions: Massachusetts General Hospital and the Medical University of South Carolina. All patients received alectinib at a starting dose of 600 mg twice daily, which is the established recommended phase II dose.[8] Consistent with prior reports, patients were considered to have LM if they had cytologically confirmed malignant cells in cerebrospinal fluid (CSF) or gadolinium-enhanced magnetic resonance imaging (MRI) consistent with LM (i.e., presence of abnormal

leptomeningeal enhancement or enhancing subarachnoid nodules).[9]

RESULTS

Case 1 involves a 56-year-old man with metastatic, *ALK*-rearranged NSCLC. A baseline MRI was negative for intracranial metastases. He was initially treated with crizotinib, achieving a significant radiographic response. Sixteen months later, however, he developed osseous metastases and multiple new, asymptomatic brain parenchymal metastases. Radiation therapy was deferred in favor of treatment with the second-generation ALK inhibitor ceritinib. Despite significant improvement of his systemic disease on ceritinib, repeat neuroimaging demonstrated progressive CNS disease, including new leptomeningeal enhancement. Soon thereafter, the patient experienced a generalized seizure, prompting treatment with corticosteroids and whole brain radiotherapy (WBRT). His post-radiation therapy course was complicated by persistent fatigue, word-finding difficulties and intermittent confusion. Ceritinib, which had been held throughout radiation, was resumed. Repeat neuroimaging 2 months later demonstrated interval improvement in numerous brain metastases, but unchanged leptomeningeal enhancement. The patient's mental status and mobility continued to decline, ultimately prompting the transition to alectinib (600 mg twice daily). Within several weeks, he experienced significant improvements in cognition, energy, and mobility. Alectinib was well tolerated without significant adverse events (AEs). Repeat imaging 2 months later demonstrated near complete resolution of leptomeningeal enhancement (Fig. 1) and stable systemic disease. The patient has remained on alectinib for 5 months with continued intracranial response.

Case 2 involves a 50-year-old man with metastatic ALK-positive NSCLC treated with first-line crizotinib. He initially responded to crizotinib, but developed grade 4 transaminase elevation, ultimately prompting discontinuation of therapy. He subsequently received carboplatin/pemetrexed, maintenance pemetrexed, and ceritinib. Notably, a pre-ceritinib brain MRI revealed asymptomatic CNS parenchymal metastases, which initially improved on therapy. Repeat neuroimaging 7 months later, however, demonstrated innumerable new brain parenchymal metastases as well as leptomeningeal enhancement. He underwent radiosurgery (Gamma Knife) to multiple target lesions followed by eventual WBRT. Four months later, the patient developed left-sided ptosis, diplopia, slurred speech, and headaches. Repeat imaging showed worsening LM, including new diffuse enhancement throughout the leptomeninges of the spine. Ceritinib was discontinued. He began alectinib in March 2014. After 3 weeks of therapy, he had dramatic improvements in headaches, speech, diplopia, and performance status. Repeat imaging 2 months later demonstrated significant interval improvement in leptomeningeal enhancement throughout the neuraxis. No significant AEs were observed while on alectinib. After 6 months of therapy, however, the patient developed recurrent neurologic symptoms. Imaging confirmed progressive LM, as well as interval progression in the liver. He was ultimately transitioned to hospice and died in October 2014.

Case 3 involves a 39-year-old woman with metastatic, ALK-positive NSCLC initially treated with cisplatin/pemetrexed (one cycle) followed by crizotinib. She remained on therapy with good systemic disease control until February 2013, when a brain MRI revealed new left parietal dural enhancement with extension into the leptomeninges. She was treated with WBRT, resuming crizotinib upon completion. Two months later, she was found to have systemic disease progression with stable neuroimaging. She subsequently received ceritinib followed by carboplatin/pemetrexed/crizotinib. In August 2014, she developed headaches, right-sided weakness, visual hallucinations and focal seizure activity. A brain MRI showed an enlarging left parietal leptomeningeal-based

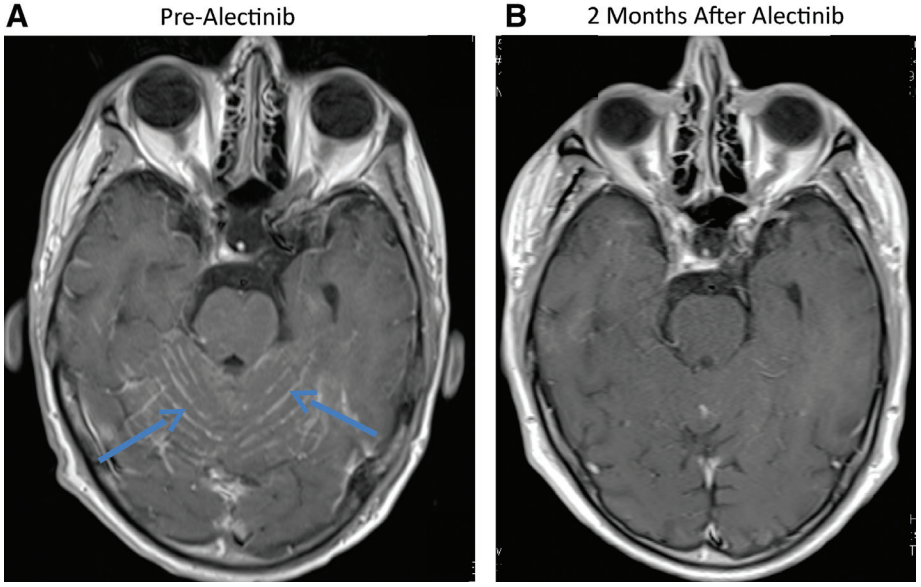

FIGURE 1. T1, post-gadolinium magnetic resonance images (MRI) depicting near complete resolution of leptomeningeal enhancement in a patient treated with alectinib. *A*, Before treatment with alectinib (*blue arrows* abnormal leptomeningeal enhancement). *B*, Two months after initiation of treatment with alectinib.

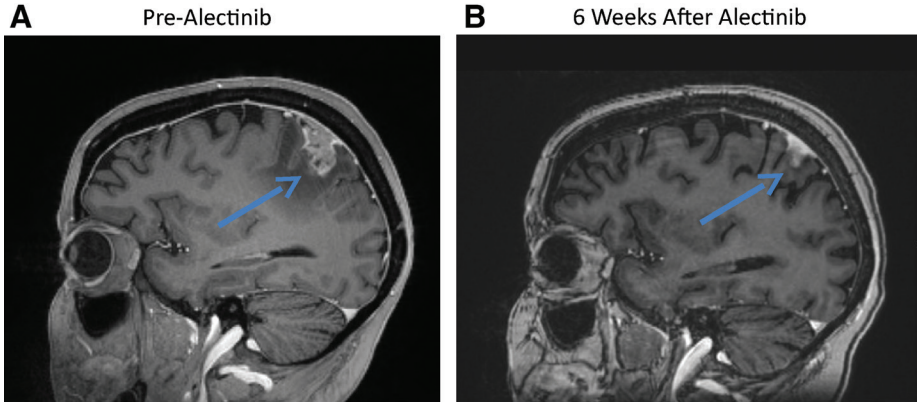

FIGURE 2. Regression of a nodular leptomeningeal metastasis in an ALK-positive patient treated with alectinib. Sagittal, T1 post-gadolinium magnetic resonance images *A*, before treatment with alectinib (*blue arrows* abnormal, nodular leptomeningeal enhancement) and *B*, 6 weeks after starting alectinib.

lesion with extension of LM enhancement (Fig. 2). She was placed on corticosteroids and levetiracetam. Intrathecal chemotherapy was deferred due to its unclear efficacy in large nodular dural-based disease. She began alectinib 600 mg twice daily. She tolerated alectinib well with no significant treatment-related AEs. Her right-sided weakness gradually improved and her seizures resolved, and her corticosteroids were tapered off. After 6 weeks of alectinib, repeat neuroimaging demonstrated significant interval reduction in nodular dural-based and LM enhancement. The patient remains on alectinib at this time with no evidence of progression in her CNS disease.

Case 4 involves a 49-year-old woman diagnosed with stage IIA (T2bN0M0) NSCLC in February 2013. She underwent surgical resection and 4 cycles of adjuvant cisplatin/pemetrexed. On October 2013, she developed pulmonary nodules and a pleural effusion, consistent with recurrent disease. ALK FISH performed on her resection specimen revealed an *ALK* rearrangement. She began treatment with crizotinib. Of note, a brain MRI performed shortly after starting crizotinib was negative for intracranial metastases. She remained on crizotinib for 7 months, transitioning to ceritinib upon disease progression. After 1 month of ceritinib, she required hospitalization for worsening fatigue, dyspnea, and dysgeusia. Brain MRI revealed innumerable brain parenchymal metastases with leptomeningeal involvement. Ceritinib was discontinued. She was started on corticosteroids and experienced an improvement in her fatigue and performance status. Upon discharge, she began alectinib 600 mg twice daily. Treatment was briefly interrupted due to grade 2 hyperbilirubinemia, which required dose reduction to 450 mg twice daily. Her CNS disease remained stable over the next 4 months; however, she ultimately developed disease progression in the chest.

DISCUSSION

LM in NSCLC have been historically associated with a dismal prognosis (median survival 3.0–4.3 months).[10,11] Importantly, patients with LM have been routinely excluded from clinical trials; thus, data on management largely comes from retrospective analyses involving heterogeneous patient populations. Common treatment strategies have included WBRT, intrathecal or systemic chemotherapy, and palliative ventriculoperitoneal shunting. Among NSCLC patients with *EGFR* mutations, "pulsatile" EGFR inhibition has also been explored, and data suggests that this achieves higher CSF drug concentrations, controlling LM in a subset of patients.[12]

In ALK-positive NSCLC, LM is present in approximately 4% of patients,[6] but the optimal management of this complication is poorly defined. Early studies focused on the use of crizotinib, which has been associated with a 12-week intracranial disease control rate of 56% in patients with untreated brain parenchymal metastases; however, only 7% of patients have objective intracranial responses.[13] It has also been recognized that the CNS is a frequent site of relapse on crizotinib, commonly in the setting of continued systemic disease control—likely reflecting a pharmacokinetic failure of therapy. Indeed, in one case report, the CSF-to-plasma ratio of crizotinib was very low (0.0026) in a patient following crizotinib administration, suggesting poor blood–brain barrier penetration.[14] Investigators have since explored using high-dose crizotinib (1000 mg once daily) or high-dose crizotinib (600 mg once daily) plus pemetrexed (900 mg/m^2) in patients with brain metastases, but such reports were small and did not include patients with LM.[15,16] Crizotinib has also been combined with intrathecal methotrexate in one report, producing cytological responses in two patients with LM; however, the relative contributions of crizotinib versus methotrexate on treatment effects in this series were unclear.[7]

Given crizotinib's limited CNS activity, emphasis has been placed on identifying new ALK inhibitors with improved CNS penetration. Here, we report a series of four ALK-positive patients with LM who experienced clinical benefit on alectinib. All four patients were diagnosed with LM based on characteristic MRI features and symptoms. Although CSF cytology has been considered the historical gold standard for LM, it has low sensitivity.[17] Contrast-enhanced MRI, with its improved visualization of the subarachnoid space, is now considered sufficient to establish the diagnosis in a patient with typical clinical features and has become the initial, and frequently sole, diagnostic tool.[9,18] Impressively, three of four patients with LM experienced radiographic and clinical improvement, whereas a fourth had stable imaging findings. In animal models, alectinib shows

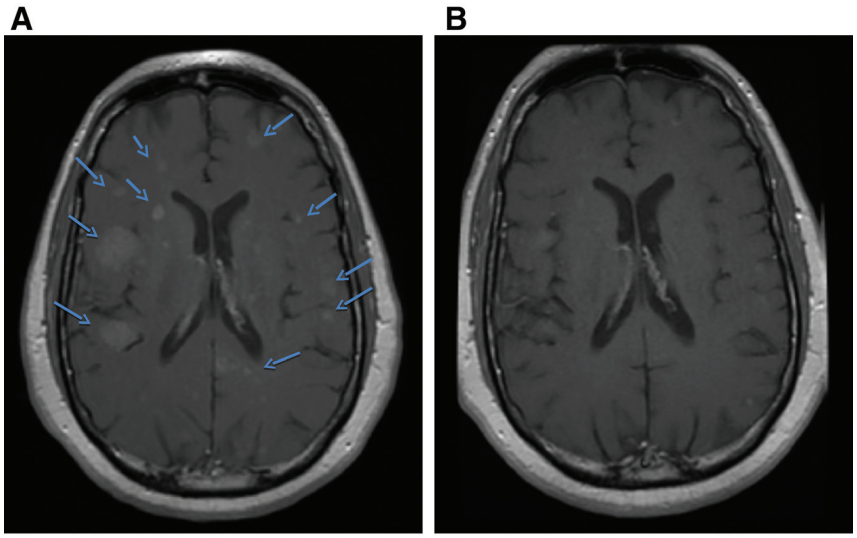

FIGURE 3. Marked regression in brain parenchymal metastases in a 46-year-old, ALK-positive lung cancer patient treated with alectinib. This patient had previously received both crizotinib and ceritinib, relapsing in the central nervous system after each agent. Axial, T1 post-gadolinium magnetic resonance images *A)* before alectinib and *B)* on alectinib.

TABLE 1. Baseline Characteristics of ALK-Positive Patients with Leptomeningeal Metastases

Pt.	Age	Sex	Prior ALK Inhibitors	Previous Radiation Therapy	Interval from Diagnosis to Development of LM	Concomitant Brain Metastases	Neurologic Symptoms
1	56	M	Crizotinib, ceritinib	WBRT	23 Months	Yes	Seizure, confusion, word-finding difficulties
2	50	M	Crizotinib, ceritinib	Radiosurgery × 2, WBRT	18 Months	Yes	Headaches, diplopia, slurred speech, nausea, ptosis
3	39	F	Crizotinib, ceritinib	WBRT	9 Months	No	Focal seizures, right-sided weakness, visual hallucinations
4	49	F	Crizotinib, ceritinib	None	16 Months	Yes	Fatigue

ALK, anaplastic lymphoma kinase; F, female; LM, leptomeningeal metastases; M, male; WBRT, whole brain radiation therapy.

high brain-to-plasma ratios (0.63–0.94) and activity in intracranial tumor implantation models.[19] In contradistinction to crizotinib and ceritinib,[20] preclinical studies also suggest that alectinib is not a substrate of *P*-glycoprotein (P-gp), a key drug efflux pump typically expressed in the blood–brain barrier.[19] Clinically, objective responses have been seen in 55% of crizotinib-resistant/intolerant patients treated with alectinib in an ongoing phase I/II trial.[8] Importantly, among 21 patients with baseline CNS lesions in this study, 52% had objective responses in the CNS. Moreover, measurable concentrations of alectinib were found in 5 of 5 patients who underwent CSF sampling, confirming the CNS penetration of alectinib.

In addition to alectinib, data on the CNS activity of other next-generation ALK inhibitors has recently emerged. For example, in an ongoing phase I/II trial of the ALK inhibitor AP26113, 10 of 14 patients (71%) with untreated/progressive brain metastases experienced intracranial tumor regressions on therapy.[21] CNS antitumor activity has also been described with ceritinib. Specifically, intracranial responses were seen in 10 of 29 patients (34.5%) who entered the phase I study of ceritinib with measurable CNS metastases.[22] More recently, radiographic improvements were also reported in an ALK-positive patient with LM who was treated with ceritinib.[23] However, as illustrated by this report, patients may relapse in the CNS despite treatment with ceritinib. Indeed, CNS concentrations of ceritinib are predicted to be approximately 15% of plasma levels based upon animal models.[24] It is therefore possible that the CNS activity of alectinib in this series may have been due to enhanced CNS bioavailability, thereby overcoming incomplete ALK inhibition.

In summary, we demonstrate that alectinib has significant antitumor activity in ALK-positive patients with LM. Moreover, alectinib was active in this cohort despite prior exposure to both crizotinib and ceritinib (the two ALK inhibitors currently approved by the FDA), suggesting that alectinib may have greater CNS activity. Of note, in addition to responses among these patients with LM, we have also observed antitumor activity in brain parenchymal metastases in a patient treated with compassionate use alectinib after CNS relapses on crizotinib and ceritinib (Fig. 3). Additional prospective studies of alectinib in ALK-positive patients with CNS metastases, including LM, are therefore warranted. Indeed, one such study, the ALEX study, is already ongoing. This phase III randomized trial is evaluating first-line crizotinib versus alectinib in treatment-naive,

ALK-positive lung cancer patients (NCT02075840). Of note, the ALEX trial permits patients with asymptomatic brain or LM to enroll. Moreover, time to CNS progression is a key secondary endpoint of the study, which may in turn provide important prospective data on the CNS antitumor activity of both agents.

As is common with targeted therapies in NSCLC, acquired resistance developed in two patients in this series, highlighting the need for additional therapies or therapeutic combinations with activity in the CNS. One approach has been to use still more potent and/or structurally distinct ALK inhibitors. For example, PF-06463922 is a novel ALK inhibitor that was recently developed and rationally designed to minimize P-gp-mediated drug efflux and optimize CNS penetration.[25] In preclinical models, this agent has shown antitumor activity in the CNS and has demonstrated strong activity against all known *ALK* resistance mutations identified in patients with crizotinib-resistant disease. Moving forward, clinical trials of novel, brain penetrable targeted therapies may help inform the optimal management of CNS metastases in advanced ALK-positive NSCLC.

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