



CNS Activity of Alectinib in Advanced ALK-Rearranged NSCLC: A Retrospective Review

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ABSTRACT

Purpose: Central nervous system (CNS) metastases are a significant contributor to morbidity and mortality in *ALK*-rearranged non-small cell lung cancer (NSCLC). While alectinib is known to have excellent CNS activity in *ALK*-rearranged NSCLC, clinical trial data are limited to patients with stable treated or asymptomatic untreated CNS metastases. Clinical outcomes of alectinib therapy in patients with untreated symptomatic, large CNS lesions remain undetermined.

Materials and Methods: Patients with advanced *ALK*-rearranged NSCLC who were treated with alectinib at the Massachusetts General Hospital Cancer Center were eligible for this study. Patients must have had untreated, active CNS metastases prior to starting alectinib or RT followed by alectinib. Medical records were retrospectively reviewed to extract data on clinicopathologic features and treatment histories. Intracranial time to progression (TTP) and overall progression-free survival (PFS) were analyzed.

Results: We identified 68 patients eligible for this study. The overall median intracranial TTP on alectinib was 19.8 months [95% confidence interval (CI), 14.7-25.4 months]. Median overall PFS was 14.5 months (95% CI, 8.4-19.1 months). The CNS disease control rate at 12 weeks was 95%. Among 24 patients in this study with untreated, active CNS metastases that were \geq 1 cm and/or symptomatic, the median overall PFS was 17.4 months (95% CI, 10.5-21.4 months) with a median intracranial TTP of 17.4 months (95% CI, 12.2.5-21.4 months). The intracranial TTP was comparable in patients regardless of the size of the largest CNS metastasis, presence of symptoms attributable to CNS disease, presence of associated radiographic edema, or steroid requirement for CNS disease.

Conclusions: Alectinib is highly effective in the treatment of CNS disease in patients with advanced *ALK*-rearranged NSCLC, including in those patients with symptomatic or large brain metastases. These findings suggest that CNS radiation could potentially be deferred in this patient population, and underscore the value of further development of ALK inhibitors with excellent CNS penetration.

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GLOSSARY OF ABBREVIATIONS

- AE adverse events
- ALK anaplastic lymphoma kinase
- AST aspartate aminotransferase
- ALT alanine aminotransferase
- CI confidence interval
- CNS central nervous system
- CTCAE Common Terminology Criteria for Adverse Events
- EGFR epidermal growth factor receptor
- NE non-estimable
- NSCLC non-small cell lung cancer
- ORR objective response rate
- OS overall survival
- PFS progression-free survival
- RT radiotherapy
- SRS stereotactic radiosurgery
- TKI tyrosine kinase inhibitor
- TTP time to progression
- WBRT whole brain radiotherapy

INTRODUCTION

Lung cancer is the leading cause of cancer death in the United States. Non-small cell lung cancers (NSCLC) comprise approximately 80% of diagnosed lung cancers.¹ A subset of NSCLCs have been found to be "oncogene-addicted," a state in which tumor cells become dependent on an oncogenic driver gene alteration for survival. This insight became clinically relevant with the advent of genotype-directed, targeted therapies, which transformed the treatment paradigm and prognosis for patients with advanced NSCLC.

Anaplastic lymphoma kinase (*ALK*) gene rearrangement represents an oncogenic fusion identified in 3-7% of NSCLCs.² *ALK* rearrangements are clinically associated with a younger age at diagnosis, never or light smoking history, and adenocarcinoma histologic type. Crizotinib, a multi-targeted MET/ALK/ROS1 tyrosine kinase inhibitor (TKI), was the first ALK-targeted therapy approved for the treatment of advanced *ALK*-rearranged NSCLC. In two randomized trials, crizotinib demonstrated significantly increased progression-free survival (PFS) and objective response rate (ORR) compared to chemotherapy in the treatment-naive and chemotherapy-pretreated settings.^{3,4} However, patients invariably experience disease relapse on crizotinib because of acquired drug resistance.⁵ Furthermore, crizotinib has suboptimal activity in the central nervous system (CNS),⁶ which is a notable limitation given the predilection of *ALK*-rearranged NSCLC to metastasize to the brain.⁷

Based on the limitations of crizotinib, efforts were launched to develop second-generation ALK TKIs with the ability to overcome the known mechanisms of resistance to crizotinib and improved ability to penetrate the CNS. Alectinib is one such second-generation ALK inhibitor which harbors activity against most of the known crizotinib-resistant *ALK* mutations.^{8,9} Of note, preclinical studies revealed that alectinib was not a substrate of the P-glycoprotein efflux transporter and had robust CNS activity in the intracranial tumor implantation models,¹⁰

suggesting its promise as a CNS-penetrant ALK TKI. Subsequently in two phase II studies, alectinib demonstrated substantial efficacy with an ORR ranging 48-50% in *ALK*-rearranged, crizotinib-pretreated NSCLC, leading to the FDA approval of alectinib in 2015 for this indication.^{11,12}

The CNS efficacy of alectinib in the clinic has been well demonstrated.^{11,12} For example, in a pooled analysis of the data from two single-arm phase II studies, alectinib had an intracranial ORR of 64%, intracranial disease control rate of 90%, and median CNS duration of response of 10.8 months in patients with baseline measurable CNS disease.¹³ However, these clinical trials notably excluded patients with symptomatic untreated CNS lesions or CNS metastases requiring steroid administration. Therefore, the ability of alectinib to control symptoms and prevent disease progression in this subset of patients remains uncharacterized.

In the clinic, referral for local therapy with radiation [e.g., whole brain radiation (WBRT) or stereotactic radiosurgery (SRS)] and/or resection followed by the initiation of an ALK TKI remains the standard of care for patients with large or symptomatic CNS metastases. Yet, CNS radiation or resection can be associated with significant short-term and long-term morbidities, including radionecrosis, somnolence, leukoencephalopathy, and neurocognitive deficits Thus, use of alectinib upfront, if effective, could offer the potential of deferring or perhaps even obviating the need for surgery or radiotherapy, allowing patients to avoid associated toxicities and delays in systemic therapy.

Here, we performed a retrospective study to determine clinical outcomes of patients with active, untreated brain and leptomeningeal metastases—including symptomatic and/or large metastases—who were treated with alectinib.

MATERIALS AND METHODS

Patients

Patients diagnosed with advanced *ALK*-rearranged NSCLC between 1/2008-1/2017 and treated at the Massachusetts General Hospital (MGH) Cancer Center were identified. Patients must have received alectinib therapy, and had baseline untreated, active CNS metastases prior to the initiation of alectinib or RT followed by alectinib. Patients with <6 months of follow-up were excluded. Additionally, patients who were treated with bevacizumab in combination with alectinib (on a clinical trial protocol at MGH) were excluded.

Data Collection

Medical records were reviewed to extract data on clinicopathologic features and treatment histories. Variables collected for analysis included the following: age, sex, race, ECOG performance status at the time of alectinib initiation, smoking history, symptoms due to CNS metastases, presence/absence of radiographic edema on brain imaging, number of CNS metastases, size of the largest CNS metastasis, presence/absence of leptomeningeal disease, whether steroids were required prior to alectinib initiation (and if so, duration of steroid use and peak steroid dose), details of prior systemic therapies and radiotherapy course(s) (e.g., dates, RT dose and fractionation), and post-alectinib treatment course. Toxicities were scored by the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. This study was approved by the Institutional Review Board (IRB) at MGH.

Statistical Analysis

Comparisons of categorical variables were conducted using a Pearson chi-square test. Intracranial TTP and overall PFS were calculated from the alectinib start date until the date of intracranial or overall progression, defined as radiographic or clinical progression. Patients without documented disease progression were censored on the date of last follow-up. Overall

survival (OS) was calculated from the alectinib start date until the date of death from any cause. Patients alive at data cut-off were censored on the date of last follow-up. The Kaplan-Meier method and log-rank tests were used to analyze TTP, PFS and OS outcomes. All statistical analyses were performed using JMP, v.11 (SAS Institute Inc., Cary, NC). P-values of less than or equal to 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

Baseline clinicopathologic and prior treatment characteristics for the 68 patients in this study cohort are summarized in Table 1. The median age at diagnosis of advanced NSCLC was 52 years. The majority of patients were never (74%) or light (16%) smokers, had adenocarcinoma histology (99%), and had stage IV disease at diagnosis (82%). Most patients (63%) had extrathoracic metastasis at diagnosis. Twenty-five patients (37%) had known CNS metastasis at diagnosis.

The median number of systemic therapies prior to alectinib was 1 (range, 0-11). Most (91%) patients received crizotinib prior to alectinib. A minority of patients (29%) were treated with a TKI other than crizotinib prior to alectinib (ceritinib, n = 18; brigatinib, n = 2). Five patients (7%) received alectinib as a first-line systemic therapy. Of the 30 patients (44%) who had prior CNS RT, 7 (10%) received both prior SRS and WBRT. The median duration between most recent RT and alectinib was 8.2 months (range, 0.6-37.5 months).

Most patients (81%) were asymptomatic from their CNS disease prior to starting alectinib. A majority of patients (72%) had four or more CNS metastases at the time of alectinib. Radiographic edema was associated with CNS metastases in a minority (28%) of patients. The median size of the largest CNS metastasis was 0.9 cm (range, 0.2-5.2 cm), with 34% of patients

with CNS metastases \geq 1cm. Thirteen patients (19%) required steroids for symptoms related to the CNS disease prior to alectinib initiation; for this cohort, the median duration of steroid use was 45.5 days (range, 18- 412 days).

Alectinib Treatment Outcomes

All but 3 patients (4%) received the standard approved dose of alectinib at 600 mg twice a day. Two patients received alectinib at reduced doses of 300 and 450 mg twice a day respectively due to enrollment in dose-escalation protocols. One patient who was initially treated at an outside institution received alectinib at a starting dose of 900 mg twice a day. Of the 48 patients who experienced disease progression on alectinib by the date of analysis, 33% (16) had CNSonly disease progression, 29% (14) had extracranial-only progression, and 38% (18) had both intra- and extracranial progression.

The median intracranial TTP on alectinib was 19.8 months (95% CI, 14.7-25.4 months) with a median overall PFS was 14.5 months (95% CI, 8.4-19.1 months) (Fig. 1). The median overall PFS for the subset of patients who received second- or greater-line alectinib was also 14.5 months (95% CI, 7.8-19.8 months). The median duration of follow-up was 22.8 months. The CNS disease control rate at 12 weeks was 95%. The majority of patients (73%) did not undergo local CNS therapy following alectinib; of those who did undergo subsequent CNS RT, the median time to RT after alectinib was 258 days (range, 62-1172 days). OS data was not yet mature, with 53 of 68 patients still alive at the time of data collection.

Alectinib in Patients with Large (≥1cm) and/or Symptomatic CNS Metastases

Twenty-four of the 68 patients in this study had untreated, active CNS metastases that were \geq 1cm, symptomatic, or both prior to starting alectinib. Clinical characteristics and outcomes of

this subset of patients are summarized in Table 2. The median size of the largest CNS metastasis in this subset of patients was 1.4 cm (range, 0.3-5.2 cm). The majority (71%) of patients had \geq 5 CNS metastases. Radiographic edema was observed with 26% of patients, and the presence of radiographic edema was significantly correlated with size of largest metastasis (p = 0.003). Among the 11 patients who were symptomatic from their CNS disease, the most common symptoms included headaches (n = 6, 25%), focal neuropathy (n = 3, 13%) and seizures (n = 2, 8%). Steroids were administered prior to alectinib initiation in 7 (29%) patients, with the median steroid duration and peak steroid dose of 48 days and 8 mg dexamethasone daily, respectively.

The median overall PFS for this subset of patients was 17.4 months (95% CI, 10.5-21.4 months), and the median intracranial TTP was 17.4 months (95% CI, 10.5-21.4 months). Nine (82%) of these 11 patients with symptoms related to the CNS disease reported experiencing symptomatic improvement upon starting alectinib. Six (25%) patients required eventual local therapy with radiation.

Next, we sought to determine whether overall PFS and intracranial TTP differed based on the size of the largest CNS metastases, presence of symptoms due to CNS disease, evidence of radiographic edema, or steroid requirement for CNS disease. There was no significant difference observed in the median overall PFS or intracranial TTP based on these criteria (Fig. 2).

Illustrative Patient Cases

Patient 1 is a male never-smoker diagnosed with stage IIIB *ALK*-rearranged lung adenocarcinoma at age 22. He was initially treated with crizotinib but experienced extracranial disease progression, at which time he switched to ceritinib. Ceritinib was discontinued due to

intolerability. The patient was subsequently lost to follow-up for 5 months, and re-presented with headaches. Imaging revealed 7 new brain metastatic lesions, the largest of which measured 5.2 cm and was associated with radiographic edema and mass effect. He was immediately initiated on alectinib 600 mg twice daily along with steroids (dexamethasone 2 mg daily with a three-week taper. He experienced resolution of his headaches and repeat brain imaging demonstrated radiographic response in the CNS. Representative images of the CNS response are depicted in Figure 3. He had stable disease systemically. Approximately 21 months after starting alectinib, he ultimately developed CNS progression. He remained on alectinib at the time of data collection for this study.

Patient 10 is a female never-smoker who was diagnosed with stage IIIA *ALK*-rearranged NSCLC at age 40. She received definitive therapy with concurrent chemotherapy and RT. However, 12 months after completing definitive therapy, she developed new headaches. Brain imaging demonstrated at least 7 brain metastases with associated edema. The largest brain metastasis measured 1.9 cm. She received steroids (peak dose of 8 mg dexamethasone daily) and was initiated on first-line alectinib, 600 mg twice a day. She had an excellent radiographic response in the brain with resolution of her CNS symptoms. Representative images are again depicted in Figure 3. Alectinib treatment was complicated by the development of grade 2 AST and ALT elevation 4 months into therapy, necessitating dose hold and eventual dose reduction to 450 mg twice a day. At the most recent follow-up approximately 12 months since the initiation of alectinib, she had resumed full dose alectinib with stable CNS and systemic disease.

Comparison of Upfront RT versus Upfront Alectinib: An Exploratory Analysis

Within the overall cohort, 60 patients (88%) received upfront alectinib for active, untreated CNS metastases, while the remaining 8 patients (12%) received upfront radiotherapy followed by alectinib. Baseline characteristics for these two subgroups of patients are compared in Table 3.

Patients who received upfront radiotherapy were more likely to have required steroids prior to starting alectinib (71% vs 16%, p = 0.0009) relative to those who directly went onto alectinib without preceding CNS RT. There was no significant difference between the two groups with respect to age, sex, race, smoking history, number of CNS metastases, presence of symptoms from CNS metastases, presence of radiographic edema, or size of the largest CNS metastasis (Table 3).

Median intracranial TTP for patients who received upfront RT was not able to be established due to a low number of progression events (95% CI, 7.3 months to non-estimable; Fig. 4), Median intracranial TTP for patients who received upfront alectinib was 19.1 months (95% CI, 14.6-24.2 months; p > 0.08). Median overall PFS was 12.8 months (95% CI, 4.4 months to nonestimable) for patients who received upfront RT, as compared to 14.5 months (95% CI, 8.4-19.1 months; p > 0.35) for patients who received upfront alectinib.

Adverse Events on Alectinib

Adverse events (AEs) experienced by the study cohort during alectinib treatment are summarized in Table 4. While a majority (93%) of patients experienced at least one AE, only 15% of patients experienced an AE of grade 3-5 per the CTCAE v4.0 criteria. An AE leading to dose interruption or dose reduction occurred in 20% and 25% of patients, respectively. The most common AEs were myalgia (43%), constipation (38%), peripheral edema (28%), and fatigue (27%). Neurologic AEs attributed to alectinib were rare; the most common were dysgeusia (7%), headache (5%), and radiation necrosis with prior/concurrent RT (3%).

DISCUSSION

In this retrospective study, we evaluated clinical outcomes in a cohort of patients with advanced *ALK*-rearranged NSCLC and active, untreated CNS metastases, who were treated with

alectinib. We found that alectinib was highly effective in this context, including in patients with large (≥1 cm) or symptomatic brain metastases. The median intracranial TTP in this cohort was 19.8 months, with a median overall PFS of 14.5 months.

Our findings support the data from prior clinical trials and pooled analyses, which demonstrated robust CNS activity of alectinib. Based on the pooled analysis of two phase II studies of alectinib in crizotinib-refractory, *ALK*-rearranged NSCLC, the CNS ORR in patients with baseline measurable CNS disease was 64% with a CNS disease control rate of 90%.¹³ The median time to CNS progression in this pooled analysis was 8.3 months. We should note that our analysis included patients treated with varying lines of alectinib, where a small number (7%) received first-line alectinib and the majority received second- or later-line alectinib. The heterogeneity of this study cohort admittedly makes it challenging to directly compare the PFS data with prior trials.

Importantly, to the best of our knowledge, this is the first study to assess the CNS efficacy of alectinib in patients with untreated, active CNS metastases that were symptomatic. The prior phase II and III trials of alectinib explicitly excluded patients with symptomatic brain metastases.^{11,12,14,15} This represents an important gap in the field bearing significant implications. Currently in the clinic, patients with symptomatic or large CNS metastases are routinely referred first for local CNS therapy (e.g., surgical resection or radiation) prior to the initiation of a CNS-penetrant ALK TKI such as alectinib.

We observed favorable clinical and radiographic outcomes in the subgroup of patients with ≥ 1 cm and/or symptomatic CNS metastases. The majority of patients experienced noticeable improvement in their neurologic symptoms following the initiation of alectinib, and the intracranial TTP for these patients was 17.4 months, not significantly different from that of the

overall cohort. Furthermore, in this study, the overall PFS and intracranial TTP were comparable in patients regardless of the size of the largest CNS metastasis, presence of symptoms related to CNS disease, presence of radiographic edema, or steroid requirement for CNS disease. Collectively, our findings suggest that clinicians may consider postponing CNS RT in favor of initiating alectinib, even in patients with significant CNS disease burden, potentially sparing the patients from experiencing short- and long-term morbidities associated with radiation.

An additional aim of our study was to determine whether there was a difference in outcomes between patients who were treated with upfront alectinib versus upfront RT followed by alectinib. Although this particular question has not yet been addressed in ALK-rearranged NSCLC, a prior study by Magnuson et al. investigated the efficacy of upfront targeted therapy with an EGFR TKI versus radiotherapy in patients with EGFR-mutant NSCLC and known brain metastases. In this prior retrospective analysis, patients treated with upfront SRS treatment had a prolonged median OS (46 months) as compared to those treated with upfront EGFR-TKI (25 months).¹⁶ It should be noted, though, that the EGFR TKIs evaluated in this analysis were erlotinib and gefitinib, both of which are first-generation EGFR TKIs with limited CNS activity compared to the third-generation EGFR TKI osimertinib. In our analysis of upfront RT versus alectinib in ALK-rearranged NSCLC, we found that the baseline characteristics of the upfront RT subgroup differed significantly from the upfront alectinib subgroup in terms of the preceding steroid requirement. This finding is not entirely surprising, as patients with greater CNS disease burden may have been more likely to be referred for upfront RT. Additionally, the number of patients who were treated with RT prior to starting alectinib was small in this study, again limiting this analysis.

This study had a number of notable limitations. First, the sample size was limited, and this was a retrospective, single-institution study. Therefore, caution is warranted when generalizing the

conclusions from this study to other institutions and treatment settings. A prospective, randomized study would be ideal to definitively address whether there is a significant difference in clinical outcomes among patients treated with upfront RT versus alectinib. However, given the growing body of evidence to support the use of upfront alectinib for the treatment of *ALK*-rearranged NSCLC with active CNS disease, a randomized controlled trial may no longer be ethically justifiable. Hence, prospective non-randomized or larger retrospective studies may be required to continue to address this question.

We note that a competing risk analysis will be beneficial in interpreting the intracranial versus systemic progression events, and this analysis is planned. We will also be pursuing an overall and intracranial objective response rate analysis utilizing the modified RECIST version 1.1. Finally, the question of the potential to delay CNS RT could be expanded to third-generation ALK inhibitors such as lorlatinib, which has similarly demonstrated excellent intracranial activity and is currently being investigated in the first-line setting in a phase III randomized controlled trial (CROWN; ClinicalTrials.gov identifier NCT03052608).¹⁷ Further data demonstrating the efficacy of upfront targeted therapies in the management of active CNS disease (including large and symptomatic brain metastases) have the potential of enabling a greater number of NSCLC patients to receive the optimal management with minimal toxicity.

SUMMARY

Central nervous system (CNS) metastases are a significant contributor to morbidity and mortality in *ALK*-rearranged non-small cell lung cancer (NSCLC). The ability of alectinib to control CNS disease in *ALK*-rearranged NSCLC has been well established. However, data in the literature are limited to patients with stable treated or asymptomatic untreated CNS metastases. There is a need for a more complete understanding of the ability of alectinib to control symptoms and prevent disease progression in patients with symptomatic, large CNS lesions.

We conducted a retrospective chart review in order to address this gap in the evidence base. We identified patients with advanced *ALK*-rearranged NSCLC who were treated with alectinib. Patients included in the study had untreated, active CNS metastases prior to starting alectinib. Medical records were retrospectively reviewed to extract data on clinicopathologic features and treatment histories. Intracranial time to progression (TTP) and overall progression-free survival (PFS) were analyzed.

Sixty-eight patients were eligible for this study. The overall median intracranial TTP on alectinib was 19.8 months (95% CI, 14.7-25.4 months). Median overall PFS was 14.5 months (95% CI, 8.4-19.1 months). The CNS disease control rate at 12 weeks was 95%. Among 24 patients in this study with untreated, active CNS metastases that were \geq 1 cm and/or symptomatic, the median overall PFS was 17.4 months (95% CI, 10.5-21.4 months) with a median intracranial TTP of 17.4 months (95% CI, 10.5-21.4 months). Intracranial TTP and overall PFS were comparable in patients regardless of the size of the largest CNS metastasis, presence of symptoms attributable to CNS disease, presence of associated radiographic edema, or steroid requirement for CNS disease.

In conclusion, alectinib has excellent CNS activity in patients with *ALK*-rearranged NSCLC who have symptomatic or large metastases. These findings suggest that clinicians may safely consider postponing CNS RT in favor of alectinib.

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$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Number of CNS metastases					
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	≥4 	49 (72%)				
$\begin{array}{c ccccc} 2 & & & 1 & (176) \\ 1 & & & 7 & (10\%) \\ 0 & & & 5 & (7\%) \end{array}$ Presence of radiographic edema $\begin{array}{c ccccccccccccccccccccccccccccccccccc$	3	6 (13%) 1 (19()				
Inknown $1 (1073)^2$ Presence of radiographic edema $5 (7\%)^2$ No $41 (72\%)$ Yes $16 (28\%)^2$ Size of the largest CNS metastasis $25 (37\%)^2$ $\leq 1 cm$ $23 (34\%)^2$ Unknown $20 (29\%)^2$ Median (cm) $0.9 (range, 0.2-5.2)^2$ Leptomeningeal disease present $61 (90\%)^2$ No $61 (90\%)^2$ Yes $7 (10\%)^2$ Steroids required prior to alectinib $45 (66\%)^2$ No $45 (66\%)^2$ Yes $13 (19\%)^2$ Unknown $10 (15\%)^2$ Median duration on steroids $45.5 days^2$	2	7 (10%)				
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Size of the largest CNS metastasis $25 (37\%)$ $\geq 1 cm$ $23 (34\%)$ Unknown $20 (29\%)$ Median (cm) $0.9 (range, 0.2-5.2)$ Leptomeningeal disease present $61 (90\%)$ Yes $7 (10\%)$ Steroids required prior to alectinib $45 (66\%)$ No $45 (66\%)$ Yes $13 (19\%)$ Unknown $10 (15\%)$ Median duration on steroids $45.5 days$	Yes	16 (28%)				
	Size of the largest CNS metastasis	05 (079()				
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Steroids required prior to alectinib45 (66%)No45 (66%)Yes13 (19%)Unknown10 (15%)Median duration on steroids45.5 days	Yes	7 (10%)				
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res 13 (19%) Unknown 10 (15%) Median duration on steroids 45.5 days	No	40 (00%) 13 (10%)				
Median duration on steroids 45.5 days	Yes	10 (15%)				
	Median duration on steroids	45.5 days				

Table 2. Clinical characteristics and outcomes of patients with CNS metastases ≥ 1 cm and/or								
Botiont	Size of		Edomo	$\frac{1-24}{2}$	Symptom	Popping	Duration of	Intracronic
Fallent	Jargest	INU.	Drocont2	attributable	Description	steroide	steroid use in	
	CNS	CNS	Fiesent:		Description	nrior to	davs (neak	(months)
	Met	Mets		met?		alectinih?	steroid dose in	(monuis)
	(cm)	INICI3		met:		alectinid:	ma	
	(011)						dexamethasone	
							per day)	
1	5.2	≥5	Y	Y	Headaches	N	-	21.4
2	2.0	. 5	N	N		N		
2	3.0	≥s	IN	IN	-	IN	-	not met
3	2.8	4	Ν	Y	Neuropathy	Ν	-	not met
4	2.8	1	Y	Y	Seizure	Y	43 (8mg)	16.1
5	26	>5	v	v	Haadaabaa	v	12(10mg)	16.0
5	2.0	20	T	T	neauaches	T	43 (12111g)	10.2
6	2.5	≥5	Y	Y	Seizure, focal	Y	37 (10mg)	12.2
		_			weakness			
7	2.3	≥5	N	N	-	Y	54 (8mg)	17.4
0	2.2	>5	N	N		V	2E(0,Emg)	10.1
0	2.2	20	IN	IN	-	T	35 (0.5mg)	19.1
9	2.1	≥5	Y	N	-	Y	66 (4mg)	10.5
10	1.9	≥5	Y	Y	Headaches	Y	5 (8mg)	not met
11	17	1	N	Ν	_	N	_	24.2
11	1.7		IN		-	IN	-	24.2
12	1.4	≥5	Ν	N	-	Ν	-	1.8
13	1.3	1	N	-	-	-	-	not met
14	13	>5	N	Ν	_	N	_	15.9
17	1.5	0	IN IN		_		_	10.5
15	1.2	≥5	Ν	N	-	Ν	-	19.8
16	1.2	≥s	N	N	-	N	-	21.4
17	1.0	>5	N	N	-	N	-	3.7
		0						0.1
18	1.0	4	Ν	N	-	Ν	-	25.4
		_						
19	1.0	≥5	N	N	-	N	-	not met
20	10	>5	N	Y	Headaches	N	-	84
20		0			riouduonoo			0.1
21	0.6	≥5	N	Y	Headaches	N	-	not met
22	0.3	1	-	Ý	Headaches	N	-	6.0
23	03	>5	N	v	Ataxia	_	_	52
20	0.0	20	IN I	'	incontinence	_	_	0.2
24	-	4	N	Y	Focal	N	-	not met
					numbness/tingling			

Table 3. Baseline characteristics for $p = 68$	patients treated with	upfront RT and upf	Table 3. Baseline characteristics for patients treated with upfront RT and upfront alectinib						
(11 – 00):	RT followed	Unfront alectinib							
	by alectinib $(n = 8)$	(n = 60)	p-value						
		(11 00)							
Median age at diagnosis (years)	56	50	0.16						
Sex									
Female	38% (3)	58% (35)	0.26						
Male	63% (5)	42% (25)							
Race									
Caucasian	100% (8)	83% (50)	0.26						
Asian	-	15% (9)							
African American	-	2% (1)							
Stage at diagnosis		000((10)	0.00						
I-III	-	20% (12)	0.06						
IV Smalling status	100% (8)	80% (48)							
Smoking status	200/ (2)	790/ (47)	0.07						
Light (100 10 pack years)	38% (3)	13% (8)	0.07						
Heavy $(>10 \text{ pack years})$	25% (2)	8% (5)							
Symptomatic CNS metastases	2070 (2)	070(0)							
No	86% (6)	80% (45)	0.73						
Yes	14% (1)	20% (11)	0110						
Number of CNS metastases									
≥5	71% (5)	71% (40)	0.21						
4	29% (2)	5% (3)							
3	-	9% (5)							
2	-	2% (1)							
1	-	13% (7)							
Radiographic edema present									
No	57% (4)	74% (37)	0.35						
Yes	43% (3)	26% (13)							
Size of largest CNS metastasis	400((0)	50%((00)	0.57						
<1cm	40% (2)	53% (23)	0.57						
≥1cm	60% (3)	47% (20)							
Median (cm)		0.9							
Steroids required prior to alectinib	20% (2)	84% (43)	0 0000						
	23 /0 (2) 71% (5)	16% (8)	0.0009						
105	11/0 (0)								

Table 4. Summary of adverse events on alectinib.		
Event	Any Grade (n = 60)	Grade 3-5 (n = 60)
Adverse event	93% (56)	15% (9)
Adverse event leading to dose interruption	20% (12)	7% (4)
Adverse event leading to dose reduction	25% (15)	8% (5)
Gastrointestinal Constipation Nausea Diarrhea Vomiting	38% (23) 12% (7) 7% (4) 3% (2)	- - - -
Changes in laboratory values from baseline Creatinine phosphokinase increase AST/ALT increase Blood bilirubin increase Blood phosphate decrease Alkaline phosphatase increase Anemia Blood creatinine increase Thrombocytopenia Neutrophil count decrease	23% (14) 18% (11) 15% (9) 5% (3) 5% (3) 3% (2) 2% (1) 2% (1) 2% (1)	3% (2) 5% (3) 2% (1) 5% (3) - - - - - -
Neurologic Dysgeusia Headache Radiation necrosis with prior/concurrent RT Photophobia Dizziness	7% (4) 5% (3) 3% (2) 2% (1) 2% (1)	- 2% (1) -
Cardiac Sinus bradycardia Pericarditis	5% (3) 2% (1)	2% (1)
Other Myalgia Peripheral edema Fatigue Sun sensitivity Weakness Arthralgia Orthostatic hypotension Weight gain	43% (26) 28% (17) 27% (16) 7% (4) 5% (3) 5% (3) 2% (1) 2% (1)	2% (1) - - - - - - - - - - -

Figure 1. Intracranial TTP and overall PFS on alectinib (n = 68).



Median intracranial TTP 19.8 months (95% CI, 14.7-25.4 months)

Median overall PFS 14.5 months (95% CI, 8.4-19.1 months)



Figure 2. Overall PFS and intracranial TTP, subgroup analyses by patient characteristics.

Overall PFS by size of largest CNS lesion (*p* > 0.41) <1 cm: 9.4 months (95%Cl,6-23.7) ≥1 cm: 17.4 months (95%Cl,12.2-21.4)



Overall PFS by presence of radiographic edema (p > 0.50)

Edema absent: 14.7 months (95%CI, 7.5-21.4) Edema present: 16.2 months (95%CI,10.8-24.8)



Overall PFS by symptoms due to CNS disease (p>0.97) Asymptomatic: 14.5 (95%Cl, 7.8-21.4) Symptomatic: 16.2 (95%Cl,6.0-23.2)



Overall PFS by steroid need for CNS disease (p > 0.67)

No steroid need: 15.9 months (95%Cl, 8.4-23.7) Steroid need: 16.1 months (95%Cl, 5.0-19.1)



Intracranial TTP by size of largest CNS lesion (p>0.89) <1 cm: 14.6 (95%CI ,7.0-NE) ≥1 cm: 19.1 (95%CI,15.9-24.2)



Intracranial TTP by presence of radiographic edema (p>0.46) Edema absent: 19.1 (95%Cl, 9.6-25.4) Edema present: 21.4 (95%Cl, 12.2-NE)

1.0 Edema absent Edema present Intracranial time to progression (%) 0.8 0.6 0.4 0.2 0.0 15 20 25 Follow-up (months) 35 40 6 5 10 30 45

Intracranial TTP by symptoms due to CNS disease (p>0.79) Asymptomatic: 19.8 (95%Cl, 14.6-25.4) Symptomatic: 16.2 (95%Cl, 6.0-NE)



Intracranial TTP by steroid need for CNS disease (p>0.53) No steroid requirement: 23.7 (95%CI,14.7-NE) Steroid requirement: 16.2 (95%CI, 10.5-NE)





Figure 3. Representative images of intracranial response in selected patients.

Representative images taken from axial post-contrast MRI axial cuts for two patients with untreated, symptomatic brain metastases who were started on alectinib. Figures 3.1, 3.2, and 3.3 depict representative post-contrast TI-weighted sequences for Patient 1 obtained at baseline, on day 28, and on day 106 of alectinib treatment, respectively. Figures 3.4, 3.5, and 3.6 depict representative post-contrast FLAIR sequences for Patient 10 obtained at baseline, on day 47, and on day 311 of alectinib treatment, respectively.

Figure 4. Intracranial TTP and Overall PFS Kaplan-Meier analysis in patients treated with upfront RT vs alectinib.



REFERENCES

¹ Key Statistics for Lung Cancer, 2017. The American Cancer Society; 2017.

² Lin JJ, Shaw AT. Resisting resistance: targeted therapies in lung cancer. *Trends in Cancer.* 2016;2(7): 350-364.

³ Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385-2394.

⁴ Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALKpositive lung cancer. *N Engl J Med*. 2014;371(23):2167-2177.

⁵ Shaw AT, Kim DW, Nakagawa K, et al. crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385-2394.

⁶ Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol*. 2011;29(15):443-445.

⁷ Yang P, Kulig K, Boland JM, et al. Worse disease-free survival in never-smokers with ALK+ lung adenocarcinoma. *J Thorac Oncol.* 2012; 7: 90–97.

⁸ Kodama, T., Hasegawa, M., Takanashi, K., et al. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. *Cancer Chemother Pharmacol.* 2014; 74(5):1023-1028.

⁹ Sakamoto, H., Tsukagushi, T., Hiroshima, S. et al. CH5424802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. *Cancer Cell.* 2011;19: 679–90.

¹⁰ Kodama, T., Tsukagushi T., Yoshida M., et al. Selective ALK inhibitor alectinib with potent antitumor activity in models of crizotinib resistance. *Cancer Lett.* 2014;351: 215–21.

¹¹ Shaw, AT, Gandhi, L, Gadgeel, S, et al. Phase 2 prospective analysis of alectinib in ALK-positive, crizotinib-resistant non-small-cell lung cancer. *Lancet Oncol*. 2016; 17(2): 234-242.

¹² Ou SH, Ahn JS, De Petris L, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. *J Clin Oncol*. 2016;34(7):661-668.
 ¹³ Gadgeel SM, Shaw AT, Govindan R, et al. Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non-small-cell lung cancer. *J Clin Oncol*. 2016;34(34):4079-4085.

¹⁴ Hida, T, Nokihara, H, Kondo, M, et al. Alectinib versus crizotinib in patients with ALKpositive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet*. 2017;1(390):29-39.

¹⁵ Peters, S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALKpositive non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):829-838.

¹⁶ Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol.* 2017;35(10):1070-1077.

¹⁷ Shaw, AT, Felip, E, Bauer TM, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol*. 2017;18(12):1590-1599.

ABSTRACT

Purpose: Central nervous system (CNS) metastases are a significant contributor to morbidity and mortality in *ALK*-rearranged non-small cell lung cancer (NSCLC). While alectinib is known to have excellent CNS activity in *ALK*-rearranged NSCLC, clinical trial data are limited to patients with stable treated or asymptomatic untreated CNS metastases. Clinical outcomes of alectinib therapy in patients with untreated symptomatic, large CNS lesions remain undetermined.

Materials and Methods: Patients with advanced *ALK*-rearranged NSCLC who were treated with alectinib at the Massachusetts General Hospital Cancer Center were eligible for this study. Patients must have had untreated, active CNS metastases prior to starting alectinib or RT followed by alectinib. Medical records were retrospectively reviewed to extract data on clinicopathologic features and treatment histories. Intracranial time to progression (TTP) and overall progression-free survival (PFS) were analyzed.

Results: We identified 68 patients eligible for this study. The overall median intracranial TTP on alectinib was 19.8 months [95% confidence interval (CI), 14.7-25.4 months]. Median overall PFS was 14.5 months (95% CI, 8.4-19.1 months). The CNS disease control rate at 12 weeks was 95%. Among 24 patients in this study with untreated, active CNS metastases that were \geq 1 cm and/or symptomatic, the median overall PFS was 17.4 months (95% CI, 10.5-21.4 months) with a median intracranial TTP of 17.4 months (95% CI, 12.2.5-21.4 months). The intracranial TTP was comparable in patients regardless of the size of the largest CNS metastasis, presence of symptoms attributable to CNS disease, presence of associated radiographic edema, or steroid requirement for CNS disease.

Conclusions: Alectinib is highly effective in the treatment of CNS disease in patients with advanced *ALK*-rearranged NSCLC, including in those patients with symptomatic or large brain metastases. These findings suggest that CNS radiation could potentially be deferred in this

patient population, and underscore the value of further development of ALK inhibitors with excellent CNS penetration.

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GLOSSARY OF ABBREVIATIONS

- AE adverse events
- ALK anaplastic lymphoma kinase
- AST aspartate aminotransferase
- ALT alanine aminotransferase
- CI confidence interval
- CNS central nervous system
- CTCAE Common Terminology Criteria for Adverse Events
- EGFR epidermal growth factor receptor
- NE non-estimable
- NSCLC non-small cell lung cancer
- ORR objective response rate
- OS overall survival
- PFS progression-free survival
- RT radiotherapy
- SRS stereotactic radiosurgery
- TKI tyrosine kinase inhibitor
- TTP time to progression
- WBRT whole brain radiotherapy

INTRODUCTION

Lung cancer is the leading cause of cancer death in the United States. Non-small cell lung cancers (NSCLC) comprise approximately 80% of diagnosed lung cancers.¹ A subset of NSCLCs have been found to be "oncogene-addicted," a state in which tumor cells become dependent on an oncogenic driver gene alteration for survival. This insight became clinically relevant with the advent of genotype-directed, targeted therapies, which transformed the treatment paradigm and prognosis for patients with advanced NSCLC.

Anaplastic lymphoma kinase (*ALK*) gene rearrangement represents an oncogenic fusion identified in 3-7% of NSCLCs.² *ALK* rearrangements are clinically associated with a younger age at diagnosis, never or light smoking history, and adenocarcinoma histologic type. Crizotinib, a multi-targeted MET/ALK/ROS1 tyrosine kinase inhibitor (TKI), was the first ALK-targeted therapy approved for the treatment of advanced *ALK*-rearranged NSCLC. In two randomized trials, crizotinib demonstrated significantly increased progression-free survival (PFS) and objective response rate (ORR) compared to chemotherapy in the treatment-naive and chemotherapy-pretreated settings.^{3,4} However, patients invariably experience disease relapse on crizotinib because of acquired drug resistance.⁵ Furthermore, crizotinib has suboptimal activity in the central nervous system (CNS),⁶ which is a notable limitation given the predilection of *ALK*-rearranged NSCLC to metastasize to the brain.⁷

Based on the limitations of crizotinib, efforts were launched to develop second-generation ALK TKIs with the ability to overcome the known mechanisms of resistance to crizotinib and improved ability to penetrate the CNS. Alectinib is one such second-generation ALK inhibitor which harbors activity against most of the known crizotinib-resistant *ALK* mutations.^{8,9} Of note, preclinical studies revealed that alectinib was not a substrate of the P-glycoprotein efflux transporter and had robust CNS activity in the intracranial tumor implantation models,¹⁰

suggesting its promise as a CNS-penetrant ALK TKI. Subsequently in two phase II studies, alectinib demonstrated substantial efficacy with an ORR ranging 48-50% in *ALK*-rearranged, crizotinib-pretreated NSCLC, leading to the FDA approval of alectinib in 2015 for this indication.^{11,12}

The CNS efficacy of alectinib in the clinic has been well demonstrated.^{11,12} For example, in a pooled analysis of the data from two single-arm phase II studies, alectinib had an intracranial ORR of 64%, intracranial disease control rate of 90%, and median CNS duration of response of 10.8 months in patients with baseline measurable CNS disease.¹³ However, these clinical trials notably excluded patients with symptomatic untreated CNS lesions or CNS metastases requiring steroid administration. Therefore, the ability of alectinib to control symptoms and prevent disease progression in this subset of patients remains uncharacterized.

In the clinic, referral for local therapy with radiation [e.g., whole brain radiation (WBRT) or stereotactic radiosurgery (SRS)] and/or resection followed by the initiation of an ALK TKI remains the standard of care for patients with large or symptomatic CNS metastases. Yet, CNS radiation or resection can be associated with significant short-term and long-term morbidities, including radionecrosis, somnolence, leukoencephalopathy, and neurocognitive deficits. Thus, use of alectinib upfront, if effective, could offer the potential of deferring or perhaps even obviating the need for surgery or radiotherapy, allowing patients to avoid associated toxicities and delays in systemic therapy.

Here, we performed a retrospective study to determine clinical outcomes of patients with active, untreated brain and leptomeningeal metastases—including symptomatic and/or large metastases—who were treated with alectinib.

MATERIALS AND METHODS

Patients

Patients diagnosed with advanced *ALK*-rearranged NSCLC between 1/2008-1/2017 and treated at the Massachusetts General Hospital (MGH) Cancer Center were identified. Patients must have received alectinib therapy, and had baseline untreated, active CNS metastases prior to the initiation of alectinib or RT followed by alectinib. Patients with <6 months of follow-up were excluded. Additionally, patients who were treated with bevacizumab in combination with alectinib (on a clinical trial protocol at MGH) were excluded.

Data Collection

Medical records were reviewed to extract data on clinicopathologic features and treatment histories. Variables collected for analysis included the following: age, sex, race, ECOG performance status at the time of alectinib initiation, smoking history, symptoms due to CNS metastases, presence/absence of radiographic edema on brain imaging, number of CNS metastases, size of the largest CNS metastasis, presence/absence of leptomeningeal disease, whether steroids were required prior to alectinib initiation (and if so, duration of steroid use and peak steroid dose), details of prior systemic therapies and radiotherapy course(s) (e.g., dates, RT dose and fractionation), and post-alectinib treatment course. Toxicities were scored by the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. This study was approved by the Institutional Review Board (IRB) at MGH.

Statistical Analysis

Comparisons of categorical variables were conducted using a Pearson chi-square test. Intracranial TTP and overall PFS were calculated from the alectinib start date until the date of intracranial or overall progression, defined as radiographic or clinical progression. Patients without documented disease progression were censored on the date of last follow-up. Overall

survival (OS) was calculated from the alectinib start date until the date of death from any cause. Patients alive at data cut-off were censored on the date of last follow-up. The Kaplan-Meier method and log-rank tests were used to analyze TTP, PFS and OS outcomes. All statistical analyses were performed using JMP, v.11 (SAS Institute Inc., Cary, NC). P-values of less than or equal to 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

Baseline clinicopathologic and prior treatment characteristics for the 68 patients in this study cohort are summarized in Table 1. The median age at diagnosis of advanced NSCLC was 52 years. The majority of patients were never (74%) or light (16%) smokers, had adenocarcinoma histology (99%), and had stage IV disease at diagnosis (82%). Most patients (63%) had extrathoracic metastasis at diagnosis. Twenty-five patients (37%) had known CNS metastasis at diagnosis.

The median number of systemic therapies prior to alectinib was 1 (range, 0-11). Most (91%) patients received crizotinib prior to alectinib. A minority of patients (29%) were treated with a TKI other than crizotinib prior to alectinib (ceritinib, n = 18; brigatinib, n = 2). Five patients (7%) received alectinib as a first-line systemic therapy. Of the 30 patients (44%) who had prior CNS RT, 7 (10%) received both prior SRS and WBRT. The median duration between most recent RT and alectinib was 8.2 months (range, 0.6-37.5 months).

Most patients (81%) were asymptomatic from their CNS disease prior to starting alectinib. A majority of patients (72%) had four or more CNS metastases at the time of alectinib. Radiographic edema was associated with CNS metastases in a minority (28%) of patients. The median size of the largest CNS metastasis was 0.9 cm (range, 0.2-5.2 cm), with 34% of patients

with CNS metastases \geq 1cm. Thirteen patients (19%) required steroids for symptoms related to the CNS disease prior to alectinib initiation; for this cohort, the median duration of steroid use was 45.5 days (range, 18- 412 days).

Alectinib Treatment Outcomes

All but 3 patients (4%) received the standard approved dose of alectinib at 600 mg twice a day. Two patients received alectinib at reduced doses of 300 and 450 mg twice a day respectively due to enrollment in dose-escalation protocols. One patient who was initially treated at an outside institution received alectinib at a starting dose of 900 mg twice a day. Of the 48 patients who experienced disease progression on alectinib by the date of analysis, 33% (16) had CNSonly disease progression, 29% (14) had extracranial-only progression, and 38% (18) had both intra- and extracranial progression.

The median intracranial TTP on alectinib was 19.8 months (95% CI, 14.7-25.4 months) with a median overall PFS was 14.5 months (95% CI, 8.4-19.1 months) (Fig. 1). The median overall PFS for the subset of patients who received second- or greater-line alectinib was also 14.5 months (95% CI, 7.8-19.8 months). The median duration of follow-up was 22.8 months. The CNS disease control rate at 12 weeks was 95%. The majority of patients (73%) did not undergo local CNS therapy following alectinib; of those who did undergo subsequent CNS RT, the median time to RT after alectinib was 258 days (range, 62-1172 days). OS data was not yet mature, with 53 of 68 patients still alive at the time of data collection.

Alectinib in Patients with Large (≥1cm) and/or Symptomatic CNS Metastases

Twenty-four of the 68 patients in this study had untreated, active CNS metastases that were \geq 1cm, symptomatic, or both prior to starting alectinib. Clinical characteristics and outcomes of

this subset of patients are summarized in Table 2. The median size of the largest CNS metastasis in this subset of patients was 1.4 cm (range, 0.3-5.2 cm). The majority (71%) of patients had \geq 5 CNS metastases. Radiographic edema was observed with 26% of patients, and the presence of radiographic edema was significantly correlated with size of largest metastasis (p = 0.003). Among the 11 patients who were symptomatic from their CNS disease, the most common symptoms included headaches (n = 6, 25%), focal neuropathy (n = 3, 13%) and seizures (n = 2, 8%). Steroids were administered prior to alectinib initiation in 7 (29%) patients, with the median steroid duration and peak steroid dose of 48 days and 8 mg dexamethasone daily, respectively.

The median overall PFS for this subset of patients was 17.4 months (95% CI, 10.5-21.4 months), and the median intracranial TTP was 17.4 months (95% CI, 10.5-21.4 months). Nine (82%) of these 11 patients with symptoms related to the CNS disease reported experiencing symptomatic improvement upon starting alectinib. Six (25%) patients required eventual local therapy with radiation.

Next, we sought to determine whether overall PFS and intracranial TTP differed based on the size of the largest CNS metastases, presence of symptoms due to CNS disease, evidence of radiographic edema, or steroid requirement for CNS disease. There was no significant difference observed in the median overall PFS or intracranial TTP based on these criteria (Fig. 2).

Illustrative Patient Cases

Patient 1 is a male never-smoker diagnosed with stage IIIB *ALK*-rearranged lung adenocarcinoma at age 22. He was initially treated with crizotinib but experienced extracranial disease progression, at which time he switched to ceritinib. Ceritinib was discontinued due to

intolerability. The patient was subsequently lost to follow-up for 5 months, and re-presented with headaches. Imaging revealed 7 new brain metastatic lesions, the largest of which measured 5.2 cm and was associated with radiographic edema and mass effect. He was immediately initiated on alectinib 600 mg twice daily along with steroids (dexamethasone 2 mg daily with a three-week taper. He experienced resolution of his headaches and repeat brain imaging demonstrated radiographic response in the CNS. Representative images of the CNS response are depicted in Figure 3. He had stable disease systemically. Approximately 21 months after starting alectinib, he ultimately developed CNS progression. He remained on alectinib at the time of data collection for this study.

Patient 10 is a female never-smoker who was diagnosed with stage IIIA *ALK*-rearranged NSCLC at age 40. She received definitive therapy with concurrent chemotherapy and RT. However, 12 months after completing definitive therapy, she developed new headaches. Brain imaging demonstrated at least 7 brain metastases with associated edema. The largest brain metastasis measured 1.9 cm. She received steroids (peak dose of 8 mg dexamethasone daily) and was initiated on first-line alectinib, 600 mg twice a day. She had an excellent radiographic response in the brain with resolution of her CNS symptoms. Representative images are again depicted in Figure 3. Alectinib treatment was complicated by the development of grade 2 AST and ALT elevation 4 months into therapy, necessitating dose hold and eventual dose reduction to 450 mg twice a day. At the most recent follow-up approximately 12 months since the initiation of alectinib, she had resumed full dose alectinib with stable CNS and systemic disease.

Comparison of Upfront RT versus Upfront Alectinib: An Exploratory Analysis

Within the overall cohort, 60 patients (88%) received upfront alectinib for active, untreated CNS metastases, while the remaining 8 patients (12%) received upfront radiotherapy followed by alectinib. Baseline characteristics for these two subgroups of patients are compared in Table 3.

Patients who received upfront radiotherapy were more likely to have required steroids prior to starting alectinib (71% vs 16%, p = 0.0009) relative to those who directly went onto alectinib without preceding CNS RT. There was no significant difference between the two groups with respect to age, sex, race, smoking history, number of CNS metastases, presence of symptoms from CNS metastases, presence of radiographic edema, or size of the largest CNS metastasis (Table 3).

Median intracranial TTP for patients who received upfront RT was not able to be established due to a low number of progression events (95% CI, 7.3 months to non-estimable; Fig. 4), Median intracranial TTP for patients who received upfront alectinib was 19.1 months (95% CI, 14.6-24.2 months; p > 0.08). Median overall PFS was 12.8 months (95% CI, 4.4 months to nonestimable) for patients who received upfront RT, as compared to 14.5 months (95% CI, 8.4-19.1 months; p > 0.35) for patients who received upfront alectinib.

Adverse Events on Alectinib

Adverse events (AEs) experienced by the study cohort during alectinib treatment are summarized in Table 4. While a majority (93%) of patients experienced at least one AE, only 15% of patients experienced an AE of grade 3-5 per the CTCAE v4.0 criteria. An AE leading to dose interruption or dose reduction occurred in 20% and 25% of patients, respectively. The most common AEs were myalgia (43%), constipation (38%), peripheral edema (28%), and fatigue (27%). Neurologic AEs attributed to alectinib were rare; the most common were dysgeusia (7%), headache (5%), and radiation necrosis with prior/concurrent RT (3%).

DISCUSSION

In this retrospective study, we evaluated clinical outcomes in a cohort of patients with advanced *ALK*-rearranged NSCLC and active, untreated CNS metastases, who were treated with

alectinib. We found that alectinib was highly effective in this context, including in patients with large (≥1 cm) or symptomatic brain metastases. The median intracranial TTP in this cohort was 19.8 months, with a median overall PFS of 14.5 months.

Our findings support the data from prior clinical trials and pooled analyses, which demonstrated robust CNS activity of alectinib. Based on the pooled analysis of two phase II studies of alectinib in crizotinib-refractory, *ALK*-rearranged NSCLC, the CNS ORR in patients with baseline measurable CNS disease was 64% with a CNS disease control rate of 90%.¹³ The median time to CNS progression in this pooled analysis was 8.3 months. We should note that our analysis included patients treated with varying lines of alectinib, where a small number (7%) received first-line alectinib and the majority received second- or later-line alectinib. The heterogeneity of this study cohort admittedly makes it challenging to directly compare the PFS data with prior trials.

Importantly, to the best of our knowledge, this is the first study to assess the CNS efficacy of alectinib in patients with untreated, active CNS metastases that were symptomatic. The prior phase II and III trials of alectinib explicitly excluded patients with symptomatic brain metastases.^{11,12,14,15} This represents an important gap in the field bearing significant implications. Currently in the clinic, patients with symptomatic or large CNS metastases are routinely referred first for local CNS therapy (e.g., surgical resection or radiation) prior to the initiation of a CNS-penetrant ALK TKI such as alectinib.

We observed favorable clinical and radiographic outcomes in the subgroup of patients with ≥ 1 cm and/or symptomatic CNS metastases. The majority of patients experienced noticeable improvement in their neurologic symptoms following the initiation of alectinib, and the intracranial TTP for these patients was 17.4 months, not significantly different from that of the

overall cohort. Furthermore, in this study, the overall PFS and intracranial TTP were comparable in patients regardless of the size of the largest CNS metastasis, presence of symptoms related to CNS disease, presence of radiographic edema, or steroid requirement for CNS disease. Collectively, our findings suggest that clinicians may consider postponing CNS RT in favor of initiating alectinib, even in patients with significant CNS disease burden, potentially sparing the patients from experiencing short- and long-term morbidities associated with radiation.

An additional aim of our study was to determine whether there was a difference in outcomes between patients who were treated with upfront alectinib versus upfront RT followed by alectinib. Although this particular question has not yet been addressed in ALK-rearranged NSCLC, a prior study by Magnuson et al. investigated the efficacy of upfront targeted therapy with an EGFR TKI versus radiotherapy in patients with EGFR-mutant NSCLC and known brain metastases. In this prior retrospective analysis, patients treated with upfront SRS treatment had a prolonged median OS (46 months) as compared to those treated with upfront EGFR-TKI (25 months).¹⁶ It should be noted, though, that the EGFR TKIs evaluated in this analysis were erlotinib and gefitinib, both of which are first-generation EGFR TKIs with limited CNS activity compared to the third-generation EGFR TKI osimertinib. In our analysis of upfront RT versus alectinib in ALK-rearranged NSCLC, we found that the baseline characteristics of the upfront RT subgroup differed significantly from the upfront alectinib subgroup in terms of the preceding steroid requirement. This finding is not entirely surprising, as patients with greater CNS disease burden may have been more likely to be referred for upfront RT. Additionally, the number of patients who were treated with RT prior to starting alectinib was small in this study, again limiting this analysis.

This study had a number of notable limitations. First, the sample size was limited, and this was a retrospective, single-institution study. Therefore, caution is warranted when generalizing the

conclusions from this study to other institutions and treatment settings. A prospective, randomized study would be ideal to definitively address whether there is a significant difference in clinical outcomes among patients treated with upfront RT versus alectinib. However, given the growing body of evidence to support the use of upfront alectinib for the treatment of *ALK*-rearranged NSCLC with active CNS disease, a randomized controlled trial may no longer be ethically justifiable. Hence, prospective non-randomized or larger retrospective studies may be required to continue to address this question.

We note that a competing risk analysis will be beneficial in interpreting the intracranial versus systemic progression events, and this analysis is planned. We will also be pursuing an overall and intracranial objective response rate analysis utilizing the modified RECIST version 1.1. Finally, the question of the potential to delay CNS RT could be expanded to third-generation ALK inhibitors such as lorlatinib, which has similarly demonstrated excellent intracranial activity and is currently being investigated in the first-line setting in a phase III randomized controlled trial (CROWN; ClinicalTrials.gov identifier NCT03052608).¹⁷ Further data demonstrating the efficacy of upfront targeted therapies in the management of active CNS disease (including large and symptomatic brain metastases) have the potential of enabling a greater number of NSCLC patients to receive the optimal management with minimal toxicity.

SUMMARY

Central nervous system (CNS) metastases are a significant contributor to morbidity and mortality in *ALK*-rearranged non-small cell lung cancer (NSCLC). The ability of alectinib to control CNS disease in *ALK*-rearranged NSCLC has been demonstrated. However, data in the literature are limited to patients with stable treated or asymptomatic untreated CNS metastases. There is a need for a more complete understanding of the ability of alectinib to control symptoms and prevent disease progression in patients with symptomatic, large CNS lesions.

We conducted a retrospective chart review in order to address this gap in the evidence base. We identified patients with advanced *ALK*-rearranged NSCLC who were treated with alectinib. Patients included in the study had untreated, active CNS metastases prior to starting alectinib. Medical records were retrospectively reviewed to extract data on clinicopathologic features and treatment histories. Intracranial time to progression (TTP) and overall progressionfree survival (PFS) were analyzed.

68 patients were eligible for this study. The overall median intracranial TTP on alectinib was 19.8 months (95% CI, 14.7-25.4 months). Median overall PFS was 14.5 months (95% CI, 8.4-19.1 months). The CNS disease control rate at 12 weeks was 95%. Among 24 patients in this study with untreated, active CNS metastases that were \geq 1 cm and/or symptomatic, the median overall PFS was 17.4 months (95% CI, 10.5-21.4 months) with a median intracranial TTP of 17.4 months (95% CI, 10.5-21.4 months). Intracranial TTP and overall PFS were comparable in patients regardless of the size of the largest CNS metastasis, presence of symptoms attributable to CNS disease, presence of associated radiographic edema, or steroid requirement for CNS disease.

In conclusion, alectinib has excellent CNS activity in patients with ALK-rearranged NSCLC who have symptomatic or large metastases. These findings suggest that clinicians can consider postponing CNS RT in favor of alectinib.

Table 1. Patient demographics and clinical characteristics (n = 68).					
Median age at diagnosis	52 years (range, 19-75)				
Sex	00 (50%)				
Female	38 (56%)				
Race	30 (44%)				
Caucasian	58 (85%)				
Asian	9 (13%)				
African American	1 (1%)				
Smoking status					
Never (<100 cigarettes)	50 (74%)				
Light (100 cigarettes – 10 pack-years)	11 (16%)				
Heavy (>10 pack-years)	7 (10%)				
Histology	67 (00%)				
Not otherwise specified	1 (1%)				
Stage at diagnosis	1 (170)				
I-III	12 (18%)				
IV	56 (82%)				
Extrathoracic metastasis at diagnosis					
Yes	43 (63%)				
No	25 (37%)				
CNS metastasis at diagnosis					
Yes	25 (37%)				
NU Baseline brain imaging not performed	27 (40%) 16 (23%)				
	10 (23 %)				
1	5 (7%)				
2	32 (47%)				
3	30 (29%)				
4 or greater	11 (16%)				
Prior RT					
None	38 (56%)				
SRS	13 (19%)				
WBR I	10 (15%)				
SRS and WBRT	7 (10%)				
<3 months	13% (9)				
3-6 months	7% (5)				
>6 months	23% (16)				
No prior RT	56% (38)				
Median	6.7 months (range, 0.5-31.5)				
Presence of symptoms due to CNS disease					
Symptomatic	12 (19%)				
Asymptomatic	51 (81%)				
Prior CNS metastasis resection	8 (12%)				
No	60 (88%)				
Number of CNS metastases					
≥4	49 (72%)				
3	6 (13%)				
2	1 (1%)				
1	7 (10%)				
Unknown	5 (7%)				
Presence of radiographic edema					
No	41 (72%)				
Yes Circ of the langest CNC metastasis	16 (28%)				
Size of the largest CNS metastasis	25 (37%)				
	23 (34%)				
∠ rom Unknown	20 (29%)				
Median (cm)	0.9 (range, 0.2-5.2)				
Leptomeningeal disease present					
No	61 (90%)				
Yes	7 (10%)				
Steroids required prior to alectinib					
No	45 (66%)				
Yes	13 (19%)				
Unknown	10 (15%) 45 5 days				
Median duration on steroids	40.0 uays				

Table 2. Clinical characteristics and outcomes of patients with CNS metastases ≥ 1 cm and/or								
Sympto	symptomatic CNS metastases (n = 24).							
Fallent	Jargest	INU.	Drocont?	attributable	Description	steroide	steroid use in	
	CNS	CNS	Fiesent:		Description	nrior to	davs (neak	(months)
	Met	Mets		met?		alectinih?	steroid dose in	(monuis)
	(cm)	Wiets		moti		alcound	ma	
	(011)						dexamethasone	
							per day)	
1	5.2	≥5	Y	Y	Headaches	N	-	21.4
_		_						
2	3.0	≥5	N	N	-	N	-	not met
3	2.8	4	Ν	Y	Neuropathy	N	-	not met
Ū.								
4	2.8	1	Y	Y	Seizure	Y	43 (8mg)	16.1
		-						
5	2.6	≥5	Y	Y	Headaches	Y	43 (12mg)	16.2
6	2.5	>5	v	v	Seizure focal	v	37 (10mg)	12.2
0	2.0	20	'		weakness	'	or (rong)	12.2
7	2.3	≥5	Ν	N	-	Y	54 (8mg)	17.4
		_						
8	2.2	≥5	N	N	-	Y	35 (0.5mg)	19.1
0	2.1	>5	v	N		V	66 (4mg)	10.5
9	2.1	20	I	IN	-	I	00 (4mg)	10.5
10	1.9	≥5	Y	Y	Headaches	Y	5 (8mg)	not met
11	1.7	1	N	N	-	N	-	24.2
12	1 /	>5	N	N	_	N	_	1.8
12	1.4	20	IN		-	IN	-	1.0
13	1.3	1	Ν	-	-	-	-	not met
		_						
14	1.3	≥5	N	N	-	N	-	15.9
15	12	>5	N	Ν	_	N	_	19.8
10	1.2	0	IN IN		_		_	15.0
16	1.2	≥5	Ν	N	-	Ν	-	21.4
		_						
17	1.0	≥5	N	N	-	N	-	3.7
18	10	4	N	Ν	_	N	_	25.4
10	1.0	-						20.4
19	1.0	≥5	Ν	N	-	Ν	-	not met
20	1.0	≥5	N	Y	Headaches	N	-	8.4
21	0.6	<u>\</u> 5	N	~	Headaches	N	_	not mot
~ 1	0.0	20	IN		I IEAUAUIIES	IN	-	normer
22	0.3	1	-	Y	Headaches	N	-	6.0
23	0.3	≥5	N	Y	Ataxia,	-	-	5.2
0.1		_			incontinence			
24	-	4	IN	Ý	FOCAI	N	-	not met
					านทางกองจ/แกษแกษ			

Table 3. Baseline characteristics for p	patients treated with	upfront RT and upf	ront alectinib
(n = 68).	DT fellowed	Linfrant algeticit	
	RT 10110Wed by electivity $(n = 0)$	Upfront alectinib $(n = 60)$	n velue
	by aleculitio (II – 6)	(11 – 00)	p-value
Median age at diagnosis (years)	56	50	0 16
Sex			0.10
Female	38% (3)	58% (35)	0.26
Male	63% (5)	42% (25)	
Race			
Caucasian	100% (8)	83% (50)	0.26
Asian	-	15% (9)	
African American	-	2% (1)	
Stage at diagnosis			
1-111	-	20% (12)	0.06
IV	100% (8)	80% (48)	
Smoking status			
Never (<100 cigarettes)	38% (3)	78% (47)	0.07
Light (100 – 10 pack years)	38% (3)	13% (8)	
Heavy (>10 pack years)	25% (2)	8% (5)	
Symptomatic CNS metastases		000/ (45)	0.70
	00% (0)	00% (43) 20% (11)	0.75
Number of CNS metastases	14 /0 (1)	2070(11)	
	71% (5)	71% (10)	0.21
≥5 ∧	29% (2)	5% (3)	0.21
3	-	9% (5)	
2	-	2% (1)	
1	-	13% (7)	
Radiographic edema present			
No	57% (4)	74% (37)	0.35
Yes	43% (3)	26% (13)	
Size of largest CNS metastasis			
<1cm	40% (2)	53% (23)	0.57
≥1cm	60% (3)	47% (20)	
Median (cm)	1	0.9	
Steroids required prior to alectinib			
No	29% (2)	84% (43)	0.0009
Yes	71% (5)	16% (8)	

Table 4. Summary of adverse events on alectinib.		
Event	Any Grade (n = 60)	Grade 3-5 (n = 60)
Adverse event	93% (56)	15% (9)
Adverse event leading to dose interruption	20% (12)	7% (4)
Adverse event leading to dose reduction	25% (15)	8% (5)
Gastrointestinal Constipation Nausea Diarrhea Vomiting	38% (23) 12% (7) 7% (4) 3% (2)	- - - -
Changes in laboratory values from baseline Creatinine phosphokinase increase AST/ALT increase Blood bilirubin increase Blood phosphate decrease Alkaline phosphatase increase Anemia Blood creatinine increase Thrombocytopenia Neutrophil count decrease	23% (14) 18% (11) 15% (9) 5% (3) 5% (3) 3% (2) 2% (1) 2% (1) 2% (1)	3% (2) 5% (3) 2% (1) 5% (3) - - - - -
Neurologic Dysgeusia Headache Radiation necrosis with prior/concurrent RT Photophobia Dizziness	7% (4) 5% (3) 3% (2) 2% (1) 2% (1)	- 2% (1) -
Cardiac Sinus bradycardia Pericarditis	5% (3) 2% (1)	2% (1)
Other Myalgia Peripheral edema Fatigue Sun sensitivity Weakness Arthralgia Orthostatic hypotension Weight gain	43% (26) 28% (17) 27% (16) 7% (4) 5% (3) 5% (3) 2% (1) 2% (1)	2% (1) - - - - - - - - - - -

Figure 1. Intracranial TTP and overall PFS on alectinib (n = 68).



Median intracranial TTP 19.8 months (95% CI, 14.7-25.4 months)

Median overall PFS 14.5 months (95% CI, 8.4-19.1 months)



Figure 2. Overall PFS and intracranial TTP, subgroup analyses by patient characteristics.

Overall PFS by size of largest CNS lesion (*p* > 0.41) <1 cm: 9.4 months (95%Cl,6-23.7) ≥1 cm: 17.4 months (95%Cl,12.2-21.4)



Overall PFS by presence of radiographic edema (p > 0.50)

Edema absent: 14.7 months (95%CI, 7.5-21.4) Edema present: 16.2 months (95%CI,10.8-24.8)



Overall PFS by symptoms due to CNS disease (p>0.97) Asymptomatic: 14.5 (95%Cl, 7.8-21.4) Symptomatic: 16.2 (95%Cl,6.0-23.2)



Overall PFS by steroid need for CNS disease (p > 0.67)

No steroid need: 15.9 months (95%Cl, 8.4-23.7) Steroid need: 16.1 months (95%Cl, 5.0-19.1)



Intracranial TTP by size of largest CNS lesion (p>0.89) <1 cm: 14.6 (95%CI ,7.0-NE) ≥1 cm: 19.1 (95%CI,15.9-24.2)



Intracranial TTP by presence of radiographic edema (p>0.46) Edema absent: 19.1 (95%CI, 9.6-25.4) Edema present: 21.4 (95%CI, 12.2-NE)



Intracranial TTP by symptoms due to CNS disease (p>0.79) Asymptomatic: 19.8 (95%Cl, 14.6-25.4) Symptomatic: 16.2 (95%Cl, 6.0-NE)



Intracranial TTP by steroid need for CNS disease (p>0.53) No steroid requirement: 23.7 (95%CI,14.7-NE) Steroid requirement: 16.2 (95%CI, 10.5-NE)





Figure 3. Representative images of intracranial response in selected patients.

Representative images taken from axial post-contrast MRI axial cuts for two patients with untreated, symptomatic brain metastases who were started on alectinib. Figures 3.1, 3.2, and 3.3 depict representative post-contrast TI-weighted sequences for Patient 1 obtained at baseline, on day 28, and on day 106 of alectinib treatment, respectively. Figures 3.4, 3.5, and 3.6 depict representative post-contrast FLAIR sequences for Patient 10 obtained at baseline, on day 47, and on day 311 of alectinib treatment, respectively.

Figure 4. Intracranial TTP and Overall PFS Kaplan-Meier analysis in patients treated with upfront RT vs alectinib.



Overall PFS (p > 0.35)



References

¹ Key Statistics for Lung Cancer, 2017. The American Cancer Society; 2017.

² Lin JJ, Shaw AT. Resisting resistance: targeted therapies in lung cancer. *Trends in Cancer.* 2016;2(7): 350-364.

³ Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385-2394.

⁴ Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371(23):2167-2177.

⁵ Shaw AT, Kim DW, Nakagawa K, et al. crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385-2394.

⁶ Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol*. 2011;29(15):443-445.

⁷ Yang P, Kulig K, Boland JM, et al. Worse disease-free survival in never-smokers with ALK+ lung adenocarcinoma. *J Thorac Oncol.* 2012; 7: 90–97.

⁸ Kodama, T., Hasegawa, M., Takanashi, K., et al. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. *Cancer Chemother Pharmacol.* 2014; 74(5):1023-1028.

⁹ Sakamoto, H., Tsukagushi, T., Hiroshima, S. et al. CH5424802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. *Cancer Cell.* 2011;19: 679–90.

¹⁰ Kodama, T., Tsukagushi T., Yoshida M., et al. Selective ALK inhibitor alectinib with potent antitumor activity in models of crizotinib resistance. *Cancer Lett.* 2014;351: 215–21.

¹¹ Shaw, AT, Gandhi, L, Gadgeel, S, et al. Phase 2 prospective analysis of alectinib in ALK-positive, crizotinib-resistant non-small-cell lung cancer. *Lancet Oncol.* 2016; 17(2): 234-242.

¹² Ou SH, Ahn JS, De Petris L, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. *J Clin Oncol*. 2016;34(7):661-668.

¹³ Gadgeel SM, Shaw AT, Govindan R, et al. Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non-small-cell lung cancer. *J Clin Oncol*. 2016;34(34):4079-4085.

¹⁴ Hida, T, Nokihara, H, Kondo, M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet*. 2017;1(390):29-39.

¹⁵ Peters, S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):829-838.
 ¹⁶ Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of brain metastases in

¹⁶ Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol.* 2017;35(10):1070-1077.

¹⁷ Shaw, AT, Felip, E, Bauer TM, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol.* 2017;18(12):1590-1599.