ORIGINAL ARTICLE

Efficacy and Safety of Dose-Escalated Alectinib in Patients With Metastatic ALK-Positive NSCLC and Central Nervous System Relapse on Standard-Dose Alectinib

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ABSTRACT

Introduction: Central nervous system (CNS) metastases remain a common challenge in patients with ALK-positive NSCLC. We previously reported reinduction of CNS responses using dose-intensified alectinib in two patients with CNS progression on standard-dose alectinib. Nevertheless, this strategy has not been assessed in larger cohorts.

Methods: Patients were eligible for this retrospective study if they had metastatic ALK-positive NSCLC with CNS relapse on alectinib 600 mg twice daily dosing and subsequently received escalated dosing (900 mg twice daily) of alectinib. CNS efficacy was assessed per the modified Response Evaluation Criteria in Solid Tumors version 1.1.

Results: Among 27 patients, median duration of dose-escalated alectinib was 7.7 months (95% confidence interval [CI]: 4.8–10.9), with median overall time-to-progression (TTP) of 7.1 months (95% CI: 4.4–9.6). Among 25 CNS response-assessable patients, CNS objective response rate was 12.0% (95% CI: 2.5–31.2) and CNS disease control rate was 92.0% (95% CI: 74.0–99.0), with median CNS duration of disease control of 5.3 months (95% CI: 3.4–8.3) and median CNS TTP of 7.1 months (95% CI: 4.4–9.6). Among four patients with measurable CNS disease at baseline, three experienced a best intracranial response of stable disease and one experienced intracranial partial response with CNS TTP ranging from 4.1 to 7.7 months. No patient required drug discontinuation due to treatment-related adverse event or experienced grade 3 or higher treatment-related adverse events.

Conclusions: Dose-intensified alectinib was found to have tolerability and activity in patients with ALK-positive NSCLC who experienced CNS relapse on standard-dose alectinib and represents one clinically viable strategy for this population.

Keywords: Alectinib; CNS; Brain metastases; ALK; NSCLC

Introduction

ALK gene fusions are the oncogenic driver in approximately 3% to 5% of patients with NSCLC.[1,2] In patients with *ALK* fusion-positive ("ALK-positive") NSCLC, brain metastases occur at a high frequency both at initial diagnosis (approaching 40%) and cumulatively during disease course (up to 70% at 5 y), associated with substantial morbidity and mortality.[3–6] Several second-

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and third-generation ALK tyrosine kinase inhibitors (TKIs) (e.g., alectinib, brigatinib, and lorlatinib) were found to have efficacy including central nervous system (CNS) activity in patients with metastatic ALK-positive NSCLC and represent the current standard first-line therapy.[7–9] Nevertheless, despite the CNS efficacy of these ALK TKIs, disease relapses in the CNS remain a common clinical challenge with limited subsequent therapeutic options.[10,11]

Alectinib, a second-generation ALK TKI, is one of the preferred initial therapies for patients with advanced ALK-positive NSCLC.[7] Although the Food and Drug Administration–approved dosing of alectinib (and standard dosing outside of Japan) is 600 mg twice daily, the maximum tolerated dose was not reached in the phase 1 dose-finding study of alectinib, with doses up to 900 mg twice daily explored and found to yield higher drug exposures.[12] Notably, our group previously reported the reinduction of CNS responses achieved using dose intensification of alectinib to 900 mg twice daily in two patients with metastatic ALK+ NSCLC who had experienced CNS progression on standard-dose alectinib.[13]

Here, we aimed to determine the efficacy and safety of dose-escalated alectinib in a larger cohort of patients with prior CNS disease progression on standard-dose alectinib.

Materials and Methods

Patients and Data Collection

Patients were eligible if they (1) had a diagnosis of metastatic ALK-positive NSCLC, (2) experienced progression of CNS metastases while on standard-dose alectinib (600 mg twice daily), and (3) received subsequent treatment with dose-escalated alectinib (900 mg twice daily) between July 2015 and June 2022. Patients could have previously received other ALK TKI(s), chemotherapy, or CNS-directed local therapies including radiotherapy (RT). Prior CNS-directed RT was allowed if the above-mentioned criteria were met with unequivocal CNS tumor progression post-RT. Patient data and imaging were retrospectively reviewed using electronic medical records. The treatment was administered using commercial alectinib supply for all patients after informed consent was obtained by the treating physician. One patient briefly received dose-escalated alectinib on a phase I and II trial of alectinib (NCT01871805) and then transitioned to a commercial supply, with informed consent. The study was performed under an institutional review board–approved protocol. The data cutoff date was January 31, 2023.

Assessments

Tumor responses were determined by radiologists (J.K. and S.R.D.) per the modified Response Evaluation Criteria in Solid Tumors version 1.1, which include up to five intracranial ($\geq$ 5 mm) and up to five extracranial target lesions.[14,15] The modified Response Evaluation Criteria in Solid Tumors version 1.1 permit assessment of responses in patients with small brain metastases which are not uncommon in patients with metastatic lung cancer. Brain magnetic resonance imaging was required for CNS disease assessment; computed tomography imaging was used for extracranial disease assessment. All imaging obtained at baseline and at clinically determined intervals (ranging from every 1 to 3 mo) up to treatment discontinuation were reviewed. Treatment-related adverse events (TRAEs) were graded per the Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

CNS disease control rate (DCR) was defined as the percentage of patients who had a best CNS response of complete response, partial response (PR), or stable disease. CNS objective response rate (ORR) and CNS DCR were estimated with a 95% confidence interval (CI) based on the exact binomial distribution. CNS duration of response (DOR) was defined as the time from the first scan of CNS response to CNS progression. Duration of CNS disease control was defined as the time from the first scan of CNS response or stable disease to CNS progression. CNS time-to-progression (TTP) was calculated from the start date of dose-escalated alectinib to the date of CNS progression. Overall TTP was calculated from the start of dose-escalated alectinib to the date of CNS or extracranial progression, whichever occurred earlier. Patients continuing dose-escalated alectinib without progression as of data cutoff were censored on the last follow-up date. TTP, DOR, and duration of treatment were estimated using the Kaplan-Meier method with 95% CIs calculated using the log-log transformation. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., NC).

Results

Patient Characteristics

A total of 27 patients with CNS disease progression on standard dosing of alectinib were included in this study (Table 1). At baseline, five patients (19%) had a brain metastatic lesion measuring greater than or equal to 1 cm. Eight patients (30%) had documented symptoms attributed to CNS disease, which were seizures with focal weakness (n = 1), seizures (n = 1), headaches with focal weakness (n = 1), headaches with dizziness (n = 1), confusion (n = 1), focal weakness alone (n = 1), headaches alone (n = 1), and ataxia (n = 1). Three patients (11%) required steroids for CNS disease before

Table 1. Baseline Characteristics of Patients Enrolled in the Study

Characteristics	N = 27, n (%)
Age (y),[a] median (range)	53 (31-69)
Sex	
Male	18 (67)
Female	9 (33)
Race	
White	26 (96)
Black	1 (4)
Smoking history	
Never	22 (81)
Light (<10 pack-years)	4 (15)
Heavy (≥ 10 pack-years)	1 (4)
Histological type	
Adenocarcinoma	26 (96)
Large cell neuroendocrine carcinoma	1 (4)
Prior lines of systemic therapy	
Number of prior lines of systemic therapy, median (range)	3 (1-12)
Received standard-dose alectinib immediately before dose-escalated alectinib	26 (96)
Received alectinib as the first ALK inhibitor	5 (19)
Received lorlatinib before dose-escalated alectinib	1 (4)
Received chemotherapy before standard-dose alectinib	15 (56)
Number of prior ALK inhibitors, median (range)	2 (1-4)
Pattern of progression on standard-dose alectinib	
CNS progression	26 (96)
CNS and extracranial progression	1 (4)
Previous CNS-directed RT	
None	8 (30)
SRS	12 (44)
WBRT	3 (11)
SRS and WBRT	4 (15)
Received CNS-directed RT between standard dosing alectinib and dose-escalated alectinib	9 (33)
Time since most recent CNS RT (mo), median (range)	13.9 (0.2-52.3)
Size of the largest CNS lesion	
<1 cm	22 (81)
1 cm to 2 cm	4 (15)
≥2 cm	1 (4)
Presence of symptomatic CNS metastases	
No	19 (70)
Yes	8 (30)
Presence of leptomeningeal disease	
No	19 (70)
Yes	8 (30)

[a]Age at diagnosis of advanced or metastatic NSCLC.
CNS, central nervous system; RT, radiotherapy; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

dose-escalated alectinib. All patients received alectinib dosed 900 mg twice per day. The median duration of dose-escalated alectinib therapy was 7.7 months (95% CI: 4.8–10.9) (Fig. 1*A*).

Intracranial Efficacy

Among 25 CNS response-assessable patients with measurable or nonmeasurable CNS metastases at baseline, the CNS ORR was 12.0% (95% CI: 2.5–31.2), with two patients having intracranial complete response complete responses and one with PR. CNS DCR was 92.0% (95% CI: 74.0–99.0). The median duration of CNS disease control was 5.3 months (95% CI: 3.4–8.3), with median CNS TTP of 7.1 months (95% CI: 4.4–9.6) (Supplementary Table 1; Fig. 1*B*). Of four patients with baseline measurable CNS disease, three had a best intracranial response of stable disease and one had a best response of PR, with CNS TTP of 7.7, 7.1, 6.2, and continuing at 4.1 months.

Among eight patients (30%) who had symptoms attributable to brain metastases at baseline, four had symptomatic improvement (complete resolution, n = 3; considerable reduction, n = 1). Of the eight patients, one had received local therapy (CNS stereotactic radiosurgery) before initiating dose-escalated alectinib. Eight patients (30%) in this study had leptomeningeal disease at baseline (all of whom also had parenchymal CNS metastases), and among these patients, seven had a best intracranial response of stable disease and one had PD.

Overall Efficacy

The overall DCR on dose-escalated alectinib was 77.8% (95% CI: 57.7%–91.4%) with an overall median duration of disease control of 4.4 months (95% CI: 2.1–10.9) (Supplementary Table 2). Of note, two patients had measurable extracranial disease at initiation of dose-escalated alectinib. Of these, one had partial response and one had stable disease as best extracranial tumor response. There were 21 patients (78%) who experienced disease progression on dose-escalated alectinib, of which all had CNS progression and three had extracranial in addition to CNS disease progression. The overall TTP on dose-escalated alectinib was 7.1 months (95% CI: 4.4–9.6) (Fig. 1*C*).

Safety and Tolerability

A total of 23 patients (85%) experienced grade 1 to 2 TRAEs. The most common TRAEs were anemia (52%), fatigue (37%), constipation (26%), bilirubin increase (15%), alkaline phosphatase increase (15%), peripheral neuropathy (11%), and diarrhea (11%) (Table 2). No

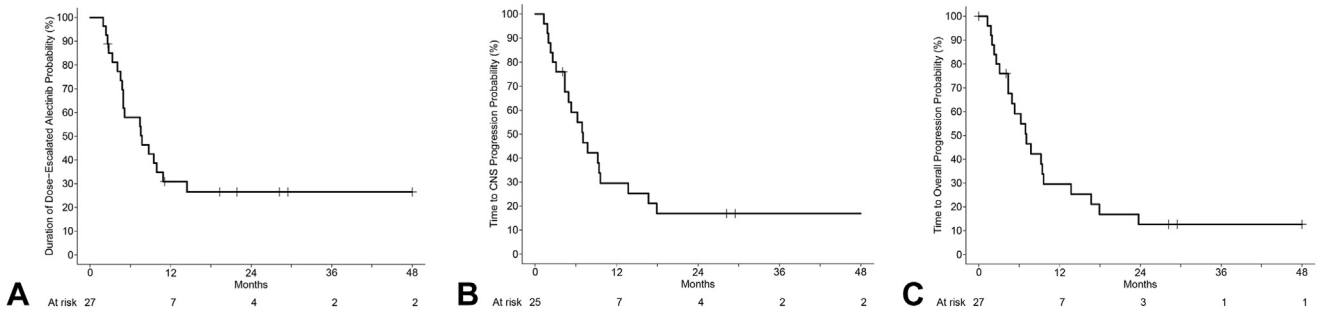

Figure 1. Efficacy of dose-escalated alectinib. (*A*) Duration of therapy on dose-escalated alectinib. (*B*) Intracranial time to progression on dose-escalated alectinib. (*C*) Overall time to progression on dose-escalated alectinib. CNS, central nervous system.

drug discontinuation due to TRAE occurred, nor were there any grade 3 or higher TRAEs. One patient required dose reduction of alectinib to 750 mg twice daily due to intolerable grade 2 fatigue, which was deemed probably related to alectinib 900 mg twice daily regimen.

Subsequent Therapies

A total of 21 patients (78%) experienced CNS relapse on dose-escalated alectinib, of which 18 patients (67%) were transitioned to subsequent therapies (Supplementary Table 3). Of note, two patients had liquid biopsies with circulating tumor DNA testing performed immediately after progression on dose-escalated alectinib, both revealing acquired *ALK* resistance mutations: I1171S (n = 1) and both I1171T and F1174L (n = 1).

There were 12 patients who subsequently received lorlatinib, a third-generation ALK TKI with known CNS penetration and efficacy.[16] In these patients, the median duration of lorlatinib therapy was 41.3 months (95% CI: 13.5–NR) with median CNS TTP of 35.2 months (95% CI: 2.2–NR) and median overall TTP of 12.8 months (95% CI: 2.2–41.3) (Supplementary Table 4; Supplementary Fig. 1). Further details on these patients and their outcomes on lorlatinib, and details on subsequent therapies for the remaining six patients, are provided in the Supplementary Material.

Discussion

In this retrospective analysis, we evaluated a cohort of patients with ALK-positive NSCLC who received dose-escalated alectinib after CNS disease relapse on standard-dose alectinib. We found that dose-escalated alectinib had meaningful efficacy with median CNS TTP of 7.1 months, overall TTP of 7.1 months, and duration of therapy of 7.7 months. Dose intensification of alectinib did not result in unanticipated toxicities, supporting the tolerability and feasibility of this regimen.

These data raise a key question of how to consider dose-escalated alectinib as a therapeutic strategy for this patient population, weighed against the alternative options, including lorlatinib, pemetrexed- or antiangiogenic agent-based regimens, or brain-directed local therapy. Lorlatinib notably represents a Food and Drug Administration–approved systemic treatment option for patients who have progressed on prior second-generation ALK TKI(s), including alectinib. In the global phase 2 study, lorlatinib yielded a compelling intracranial ORR of 56.1% and median intracranial DOR of 12.4 months in this patient population.[17] Separately, findings from a single-arm phase 2 study buttressed the durable CNS efficacy of lorlatinib in this setting, with an intracranial ORR at 12 weeks of 59% and median intracranial PFS of 24.6 months among 22 patients with CNS progression on prior ALK TKIs.[10] Although the small cohort sizes and disparate study designs preclude any direct comparisons of efficacy, consistent with the robust CNS efficacy previously reported with lorlatinib, patients in the current study who progressed on dose-escalated alectinib were able to receive subsequent lorlatinib with noteworthy benefit. These results likely reflect the differences in pharmacokinetics, with marked CNS penetration achieved by lorlatinib relative to alectinib (CSF:plasma drug concentration ratio of 0.79 for lorlatinib versus 0.3 for alectinib).[12,16] Interestingly, in this study, the median duration of subsequent lorlatinib therapy (41.3 mo) was noticeably longer compared with the median overall TTP (12.8 mo) and median CNS TTP (35.2 mo), mirroring the clinical practice of treatment beyond PD and the ability to effectively address limited disease progression with local therapies in this patient population.[18]

It remains unknown whether dose-escalated alectinib followed by lorlatinib, versus a direct switch from standard-dose alectinib to lorlatinib, represents the optimal systemic treatment approach in patients experiencing CNS disease relapse. Our findings and the available literature[10,17] suggest that a more sustained CNS benefit can be derived from the approach of switching to lorlatinib; however, other factors may bear

Table 2. Treatment-Related Adverse Events on Dose-Escalated Alectinib

Treatment-Related Adverse Events	N = 27, n (%)
Anemia	14 (52)
Fatigue	10 (37)
Constipation	7 (26)
Total bilirubin increase	4 (15)
Alkaline phosphatase increase	4 (15)
Neuropathy/balance impairment	3 (11)
Diarrhea	3 (11)
Myalgia	1 (4)
Aspartate transaminase increase	1 (4)
Alopecia	1 (4)
Peripheral edema	1 (4)
Pruritic rash	1 (4)

into treatment decision-making in the real world, including tolerability, access to therapies, and patient preference. Ultimately, the optimal approach may differ for each individual patient in real-world practice, requiring careful multidisciplinary evaluation and consideration of multiple factors such as the burden of CNS disease, systemic disease status, clinical stability, drug tolerability, and patient preference.

The strategy of TKI dose escalation has been pursued across cancers including in oncogene-addicted lung cancers specifically to achieve increased drug penetration into the brain and to rescue CNS progressive disease. As an example, in metastatic ALK+ NSCLC, a patient with multifocal CNS disease relapse on standard dosing (180 mg daily) of brigatinib experienced clinical benefit and radiologic regression of brain metastases with brigatinib dose escalated to 240 mg daily.[19] In metastatic *EGFR*-mutated NSCLC, high-dose osimertinib (160 mg daily) has been found feasible, with activity in patients experiencing intracranial progression on standard dosing (80 mg daily) of osimertinib.[20,21] For patients achieving continued extracranial disease control on a given TKI without considerable toxicities and otherwise limited alternative therapeutic options, the dose-escalation strategy offers a path for maximizing the duration of therapy and clinical benefit. The duration of CNS benefit, however, thus achieved may be modest (limited to months in range as in our series and others),[20,21] emphasizing the crucial importance of designing therapeutic agents that achieve high brain penetration at their standard dosing and can maximize upfront downstaging and—extending beyond—prevention of CNS metastases.

This study had several limitations. As mentioned, this was a single-institution, retrospective analysis of a small number of patients performed at a tertiary academic center, all serving as potential sources of bias. Given the retrospective nature of the study, the imaging frequencies were variable, and safety assessment relied on documentation within the electronic medical records. Despite these limitations, to the best of our knowledge, this study provides the first insights into the safety and efficacy of dose-escalated alectinib in a cohort of patients meeting the study criteria—an important subgroup for whom currently available therapeutic options remain limited. Another limitation is that patients could have received prior standard-dose alectinib as any line of systemic therapy, generating heterogeneity and not reflecting the current treatment paradigm where alectinib is used as a first-line therapy. Furthermore, the findings are not applicable to patients with ALK-positive NSCLC who received lorlatinib as a first-line treatment. Nevertheless, given the ongoing widespread use of alectinib as initial ALK-directed therapy globally, what constitutes viable TKI sequencing and alternative dosing strategies after alectinib (and other ALK TKIs) remain a pivotal evolving area of investigation.

In summary, dose-escalated alectinib has tolerability and activity in patients with metastatic ALK-positive NSCLC and CNS disease relapse on standard-dose alectinib. Our findings add dose intensification of alectinib as one viable strategy to the therapeutic landscape for addressing active CNS disease in ALK-positive NSCLC.

CRediT Authorship Contribution Statement

Justin M. Cheung: Conceptualization, Data curation, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review and editing.

Jiyoon Kang: Data curation, Formal analysis, Writing—review and editing.

Beow Y. Yeap: Formal analysis, Methodology, Resources, Validation, Writing—original draft, Writing—review and editing.

Jennifer L. Peterson: Data curation. Writing—review and editing

Andrew Do: Data curation, Writing—review and editing.

Justin F. Gainor: Investigation, Writing—original draft, Writing—review and editing.

Subba R. Digumarthy: Data curation, Formal analysis, Writing—review and editing.

Jessica J. Lin: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing—original draft, Writing—review and editing.

Disclosure

Dr. Gainor has served as a compensated consultant for Agios, Amgen, Array BioPharma, Blueprint Medicines, Bristol-Myers Squibb, Genentech, Gilead Sciences, ITeos

Therapeutics, Jounce Therapeutics, Karyopharm Therapeutics, Eli Lilly, Loxo, Merck, Moderna Therapeutics, Oncorus, Regeneron, and Takeda; has received honorarium from ARIAD, Incyte, Merck, Novartis, Pfizer, and Takeda; has received research funding from Adaptimmune, Alexo Therapeutics, ARIAD, Array BioPharma, AstraZeneca, Blueprint Medicines, Bristol-Myers Squibb, Genentech, Jounce Therapeutics, Merck, Moderna Therapeutics, Novartis, and Tesaro; has stock and other ownership interests in Ironwood Pharmaceuticals; and is employed by Ironwood Pharmaceuticals. Dr. Digumarthy has received honorarium from Elsevier and Siemens; received research funding from Lunit Inc., GE, QURE AI, and Vuno; is a member of the Speakers' Bureau for Siemens; and provides independent image analysis for hospital-contracted clinical trial programs for Merck, Pfizer, Bristol-Myers Squibb, Novartis, Roche, Polaris, Cascadian, AbbVie, Gradalis, Bayer, Zai Laboratories, Biengen, Resonance, and Analise. Dr. Lin has served as a compensated consultant for Genentech, C4 Therapeutics, Blueprint Medicines, Nuvalent, Bayer, Elevation Oncology, Novartis, Mirati Therapeutics, AnHeart Therapeutics, CLaiM Therapeutics, Ellipses, AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Yuhan, Merus, Regeneron, Pfizer, and Turning Point Therapeutics; received institutional research funds from Hengrui Therapeutics, Turning Point Therapeutics, Neon Therapeutics, Relay Therapeutics, Bayer, Elevation Oncology, Roche, Linnaeus Therapeutics, Nuvalent, and Novartis; and received CME funding from OncLive, MedStar Health, IDEOlogy, MLI Peerview, Gather-ed, and Northwell Health. The remainder of the authors have no conflicts of interest to declare.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100645.

References

1. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol*. 2009;27:4247–4253.
2. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*. 2007;448:561–566.
3. Gainor JF, Tseng D, Yoda S, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. *JCO Precis Oncol*. 2017;2017.
4. Drilon A, Lin JJ, Filleron T, et al. Frequency of brain metastases and multikinase inhibitor outcomes in patients with RET-rearranged lung cancers. *J Thorac Oncol*. 2018;13:1595–1601.
5. Ali A, Goffin JR, Arnold A, Ellis PM. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. *Curr Oncol*. 2013;20:e300–e306.
6. Lin HM, Pan X, Hou P, et al. Economic burden in patients with ALK + non-small cell lung cancer, with or without brain metastases, receiving second-line anaplastic lymphoma kinase (ALK) inhibitors. *J Med Econ*. 2020;23:894–901.
7. 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;377:829–838.
8. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: final results of phase 3 ALTA-1L trial. *J Thorac Oncol*. 2021;16:2091–2108.
9. Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *N Engl J Med*. 2020;383:2018–2029.
10. Dagogo-Jack I, Oxnard GR, Evangelist M, et al. Phase II study of lorlatinib in patients with anaplastic lymphoma kinase-positive lung cancer and CNS-specific relapse. *JCO Precis Oncol*. 2022;6:e2100522.
11. Bauer TM, Shaw AT, Johnson ML, et al. Brain penetration of lorlatinib: cumulative incidences of CNS and non-CNS progression with lorlatinib in patients with previously treated ALK-positive non-small-cell lung cancer. *Target Oncol*. 2020;15:55–65.
12. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. *Lancet Oncol*. 2014;15:1119–1128.
13. Gainor JF, Chi AS, Logan J, et al. Alectinib dose escalation reinduces central nervous system responses in patients with anaplastic lymphoma kinase-positive non-small cell lung cancer relapsing on standard dose alectinib. *J Thorac Oncol*. 2016;11:256–260.
14. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13:1087–1095.
15. Lin JJ, Schoenfeld AJ, Zhu VW, et al. Efficacy of platinum/pemetrexed combination chemotherapy in ALK-positive NSCLC refractory to second-generation ALK inhibitors. *J Thorac Oncol*. 2020;15:258–265.
16. 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;18:1590–1599.

17. Felip E, Shaw AT, Bearz A, et al. Intracranial and extracranial efficacy of lorlatinib in patients with ALK-positive non-small-cell lung cancer previously treated with second-generation ALK TKIs. *Ann Oncol*. 2021;32:620-630.
18. Hubbeling H, Choudhury N, Flynn J, et al. Outcomes with local therapy and tyrosine kinase inhibition in patients with ALK/ROS1/RET-rearranged lung cancers. *JCO Precis Oncol*. 2022;6:e2200024.
19. Urbanska EM, Santoni-Rugiu E, Melchior LC, Carlsen JF, Sørensen JB. Intracranial response of ALK(+) non-small-cell lung cancer to second-line dose-escalated brigatinib after alectinib discontinuation due to drug-induced hepatitis and relapse after whole brain radiotherapy followed by stereotactic radiosurgery. *Clin Lung Cancer*. 2021;22:e528-e532.
20. Goldstein IM, Roisman LC, Keren-Rosenberg S, et al. Dose escalation of osimertinib for intracranial progression in EGFR mutated non-small-cell lung cancer with brain metastases. *Neurooncol Adv*. 2020;2:vdaa125.
21. Piper-Vallillo AJ, Rotow JK, Aredo JV, et al. High-dose osimertinib for CNS progression in EGFR+ NSCLC: a multi-institutional experience. *JTO Clin Res Rep*. 2022;3:100328.