



ORIGINAL ARTICLE

Crizotinib for recurring non-small-cell lung cancer with EML4-ALK fusion genes previously treated with alectinib: A phase II trial

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Abstract

Background: The efficacy of crizotinib treatment for recurring EML4-ALK-positive non-small cell lung cancer (NSCLC) previously treated with alectinib is unclear. Based on our preclinical findings regarding hepatocyte growth factor/mesenchymal epithelial transition (MET) pathway activation as a potential mechanism of acquired resistance to alectinib, we conducted a phase II trial of the anaplastic lymphoma kinase/MET inhibitor, crizotinib, in patients with alectinib-refractory, EML4-ALK-positive NSCLC.

Methods: Patients with ALK-rearranged tumors treated with alectinib immediately before enrolling in the trial received crizotinib monotherapy. The objective response rate was the primary outcome of interest.

Results: Nine (100%) patients achieved a partial response with alectinib therapy with a median treatment duration of 6.7 months. Crizotinib was administered with a median treatment interval of 50 (range, 20–433) days. The overall response rate was 33.3% (90% confidence interval [CI]: 9.8–65.5 and 95% CI: 7.5–70.1), which did not reach the predefined criteria of 50%. Two (22%) patients who achieved a partial response had brain metastases at baseline. Progression-free survival (median, 2.2 months) was not affected by the duration of treatment with alectinib. The median survival time was 24.1 months. The most common adverse events were an increased aspartate transaminase/alanine transaminase (AST/ALT) ratio (44%) and appetite loss (33%); one patient developed transient grade 4 AST/ALT elevation, resulting in treatment discontinuation. Other adverse events were consistent with those previously reported; no treatment-related deaths occurred.

Conclusions: Although the desired response rate was not achieved, crizotinib monotherapy following treatment with alectinib showed efficacy alongside previously described adverse events.

KEYWORDS

Alectinib, anaplastic lymphoma kinase, crizotinib, drug therapy, non-small cell lung carcinoma

INTRODUCTION

The discovery of echinoderm microtubule-associated protein-like 4 (*EML4*)-anaplastic lymphoma kinase (*ALK*)

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fusion driver oncogenes has led to an evolution in treatment for advanced non-small-cell lung cancer (NSCLC)¹ and epidermal growth factor receptor (*EGFR*)-mutant tumors.² Crizotinib, the first ALK-tyrosine kinase inhibitor (TKI), has been associated with a significant survival advantage compared to standard cytotoxic chemotherapy in randomized trials.^{3,4} Subsequently, other ALK-TKIs have been introduced into clinical practice. Among them, alectinib, a relatively potent and selective ALK-TKI, is associated with substantial improvement in patient survival compared to that observed with crizotinib.^{5,6} In fact, the National Comprehensive Cancer Network guidelines⁷ now recommend alectinib as first-line ALK-TKI monotherapy for *ALK*-rearranged advanced NSCLC.

However, similar to other molecular targeted therapies, alectinib is associated with the risk of developing treatment-resistant disease.^{8–10} The mechanism of acquired resistance to crizotinib includes the development of secondary mutations in the ALK kinase domain,^{6,11–15} *ALK* gene amplification,¹¹ and bypass track activation.^{13–16} Recently, our group¹⁷ has shown that alectinib-resistant cell lines were characterized by mesenchymal epithelial transition (MET) activation induced by autocrine stimulation with hepatocyte growth factor (HGF). Moreover, once the HGF/MET pathway was activated, the cells were strongly sensitive to crizotinib in preclinical models.¹⁸ Patients with acquired resistance to alectinib, who achieved MET signaling activation, subsequently responded to crizotinib.¹⁹

The efficacy of crizotinib for recurring *EML4-ALK*-positive NSCLC previously treated with alectinib is unclear. With this background, we conducted a single-arm phase II trial to evaluate the efficacy and safety of crizotinib monotherapy in patients with *ALK*-positive, alectinib-resistant NSCLC.

METHODS

Study design, participants, and intervention

Patients were eligible for this trial if they were aged ≥ 20 years, and had an Eastern Cooperative Oncology Group performance status of 0 to 2 along with noncurable stage IIIB/IV, *ALK*-positive NSCLC with measurable disease. *ALK* status was determined by immunohistochemistry, fluorescence in situ hybridization, or a reverse transcription-polymerase chain reaction test. Patients were ALK-TKI treatment-naïve except for alectinib therapy. Patients with documented progressive disease (PD) during alectinib monotherapy and those with prior use of cytotoxic chemotherapy were included. Patients were excluded if they had symptomatic central nervous system metastases or a history of other malignancies. Patients with uncontrolled concurrent illness—including active interstitial pneumonia, pleural or pericardial effusion, or ascites—were also excluded.

Crizotinib monotherapy was administered orally at a dose of 250 mg twice daily until the occurrence of either PD

or unacceptable toxicity. Treatment interruption or dose modification was allowed if clinically justified. The protocol summary, including participant and intervention details, has been previously described.¹ Written informed consent was obtained from all patients prior to screening. This study conformed to the principles of the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of each participating site. This trial was registered in the University Hospital Medical Information Network (UMIN000015984).

Endpoint

The objective response rate (ORR) was the primary endpoint. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and the incidence of adverse events (AEs).

Statistical analysis

Our previous study¹⁸ showed that the HGF/MET pathway was activated in half of the alectinib-resistant cell lines, and a high MET expression rate was detected in 66.7% of *ALK*-positive NSCLC patients.²⁰ Thus, we expected an ORR of 50%. Since response to cytotoxic therapy was observed in approximately 20% of *ALK*-positive NSCLC cases,²¹ our lower limit of interest was fixed at 15%. The estimated accrual number was nine patients using Simon's minimax design with a one-sided α of 0.05 and β of 0.20. In addition, we conducted an interim analysis after the first four patients were registered.

RESULTS

Patients

Between June 2016 and August 2018, a total of nine patients were enrolled in this trial (Table 1). The median age of the patients was 63 years, and the most common diagnosis was adenocarcinoma (78%). All patients were treated with alectinib immediately before enrolling in the trial; seven (78%) patients received alectinib monotherapy, and two (22%) patients were treated with one or more regimens—including platinum-based chemotherapy—alongside alectinib. All nine patients achieved a partial response (PR) during alectinib therapy with a median treatment duration of 6.7 (range: 5.7–22.9) months.

Treatment delivery

The median treatment interval was 50 (range: 20–433) days (Table 2). Treatment was interrupted in three (33%) patients after a median duration of 14 (range: 3–44) days. Patients

TABLE 1 Patient demographics and clinical characteristics

Clinical factors	Patients (N = 9)
Age (years), median (range)	63 (42–80)
Sex, N (%)	
Male	3 (33)
Female	6 (67)
ECOG PS, N (%)	
0	1 (11)
1	8 (89)
Smoking history, N (%)	
Never	4 (44)
Former	2 (22)
Current	3 (33)
Tumor histology, N (%)	
Adenocarcinoma	7 (78)
Unclassified	2 (22)
Brain metastases, N (%)	
Yes	2 (22)
No	7 (78)
Prior systemic therapy, N (%)	
Alectinib only	7 (78)
Platinum and alectinib	2 (22)
Type of sample collected (<i>ALK</i> -rearrangement status), N (%)	
TBB	5 (56)
CT-guided biopsy	1 (11)
Other	3 (33)
Diagnostic test (<i>ALK</i> -rearrangement status), N (%)	
IHC	8 (89)
FISH	9 (100)
RT-PCR	0 (0)
Time from diagnosis to trial registration, months	
Median (range)	7.3 (6.1–105.1)
Treatment interval of alectinib monotherapy, months	
Median (range)	6.7 (5.7–22.9)
Objective response to alectinib monotherapy, N (%)	
PR	9 (100)

Abbreviations: *ALK*, anaplastic lymphoma kinase; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PR, partial response; RT-PCR, reverse transcription-polymerase chain reaction; TBB, transbronchial biopsy.

discontinued study treatment due to PD in seven (78%) cases, and AE or transfer to another hospital in one (11%) case each.

Efficacy

The study was continued as interim results met the preset criteria of having at least one treatment responder among the four initially registered patients. Three of the nine

TABLE 2 Characteristics of crizotinib administration

Characteristic	Patients (N = 9)
Treatment interval (days), median (range) Interruption	50 (20–433)
N (%)	3 (33)
Interval (days), median (range)	14 (3–44)
Dose reduction, N (%)	2 (22)
Discontinuation, N (%)	9 (100)
Reason	
PD	7 (78)
AEs	1 (11)
Transferred to another hospital	1 (11)

Abbreviations: AE, adverse event; PD, progressive disease.

patients responded to the study treatment; both stable disease and PD were detected in all three patients (Table 3). At this stage, the ORR was 33.3% (90% confidence interval [CI]: 9.8–65.5 and 95% CI: 7.5–70.1), which failed to meet the predefined criteria. Five (56%) patients experienced a decrease in tumor burden relative to baseline (Figure 1(a)). Among three patients, the response time duration was 5.5, 5.9, and 14.5 months, respectively. Two (22%) patients who achieved a PR had brain metastases at baseline. Days from the initiation of crizotinib monotherapy was not affected by alectinib therapy duration (paired *t*-test, *p* = 0.0411; Figure 1(b)).

For the survival analysis, the median follow-up duration was 21.2 (range: 2.8–42.6) months. The median PFS was 2.2 (range: 1.0–14.5) months (Figure 2(a)). Finally, the one-year OS rate and median survival time (MST) were 66.7% and 24.1 (range: 2.8–42.6) months, respectively (Figure 2(b)).

Safety

The most common AEs were episodes of gastrointestinal toxicity and hepatic dysfunction; appetite loss and aspartate transaminase/alanine transaminase (AST/ALT) elevation affected 33% and 44% of patients, respectively (Table 4). Moreover, one patient developed transient grade 4 AST/ALT elevation, resulting in treatment discontinuation. This complication was resolved with supportive care and did not require extensive management or admission to an intensive care unit. Myelosuppression was uncommon among patients; however, one patient had transient grade 4 neutropenia. Other AEs were consistent with the safety profile of the study agent. No treatment-related deaths were observed during the study period.

Relapse pattern and post-progression treatment

As shown in Table 5(a), all patients experienced disease recurrence, most commonly at the pre-existing site (67%).

Four (44%) patients received post-progression platinum-based therapy (Table 5(b)). The other patients received ALK-TKIs (56%); among them, one patient continued

treatment with crizotinib beyond Response Evaluation Criteria in Solid Tumors (RECIST)-defined PD, while another received alectinib monotherapy as a rechallenge regimen.

TABLE 3 Overall response

Response	Patients, N (%)
CR	0 (0)
PR	3 (33.3)
SD	3 (33.3)
PD	3 (33.3)
Overall response rate	3 (33.3)
	90% CI: 9.8–65.5
	95% CI: 7.5–70.1

Abbreviations: CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

DISCUSSION

This is the first study to demonstrate the efficacy and safety of crizotinib administered immediately after recurrence of *EML4-ALK*-positive NSCLC in patients previously treated with alectinib. In this study, the ORR was 33.3% (95% CI: 7.5–70.1), which was lower than the criterion set for the primary endpoint. Concurrently, the median PFS was 2.2 months and the MST was 24.1 months, with a one-year OS rate of 66.7%.

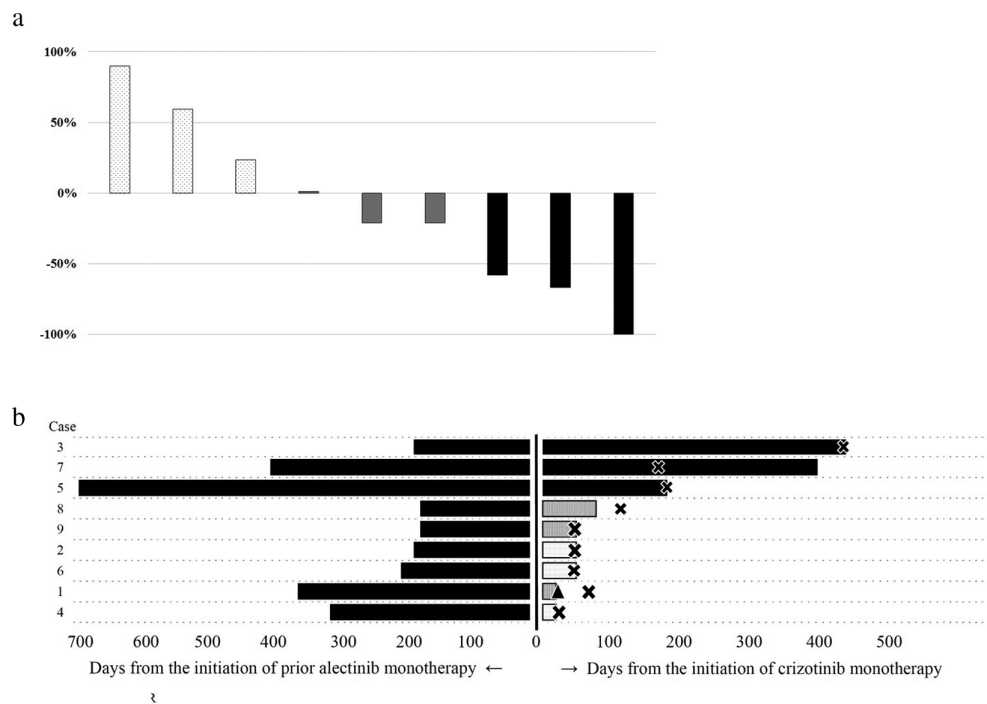


FIGURE 1 Overall response: (a) Waterfall plot. Y-axis represents the percentage change from baseline in one-dimensional measurements (sum of the diameters of target lesions); and (b) swimmer plot. Duration of treatment with alectinib (left) and crizotinib (right) immediately before registration in this trial. AE, adverse event; PD, progressive disease; PR, partial response; SD, stable disease

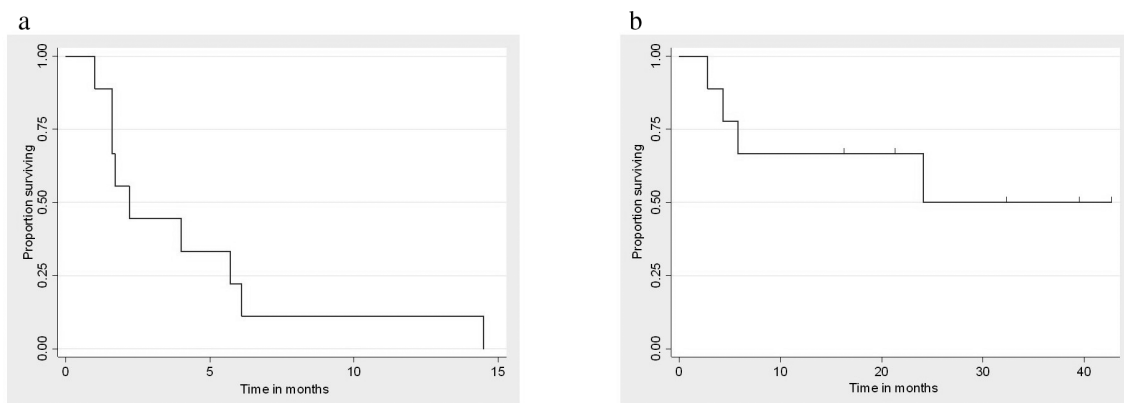


FIGURE 2 Kaplan-Meier survival curves of (a) progression-free survival (PFS); and (b) overall survival (OS). The median PFS and OS were 2.2 and 24.1 months, respectively, with a median follow-up time of 21.2 months

TABLE 4 Toxicity profiles

Event	Any grade, N (%)	Grade \geq 3, N (%)
Neutropenia	1 (11)	1 (11)
Anemia	1 (11)	0 (0)
Creatinine elevation	3 (33)	0 (0)
Fatigue	1 (11)	0 (0)
Fever	3 (33)	0 (0)
Appetite loss	3 (33)	2 (22)
Nausea/vomiting	2 (22)	1 (11)
Constipation	3 (33)	0 (0)
Diarrhea	4 (44)	0 (0)
Flashing lights	6 (67)	0 (0)
Dysgeusia	4 (44)	0 (0)
Edema	1 (11)	0 (0)
AST/ALT elevation	4 (44)	1 (11)
Hyperbilirubinemia	1 (11)	1 (11)
Pneumonitis	0 (0)	0 (0)

Note: No treatment-related deaths were observed.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 5 Recurrence sites and post-progression therapy

	Patients, N (%)
(a) Recurrence sites	
Pre-existing sites	6 (67)
New lesions	1 (11)
Both	2 (22)
(b) Subsequent post-progression therapy	
Platinum-based regimens	4 (44)
ALK-TKIs	5 (56)
Ceritinib	3 (33)
Alectinib ^{aa}	1 (11)
Crizotinib ^{bb}	1 (11)

Abbreviations: ALK, anaplastic lymphoma kinase; PD, progressive disease; TKI, tyrosine kinase inhibitor.

^aRechallenge.

^bBeyond PD use.

The ORR in this study (Table 6) was comparable to that reported in studies of other ALK-TKIs.^{22–24} Secondary ALK mutations such as G1202R and I1171T/N/S^{25,26} have been proposed to account for half of the observed alectinib resistance.²⁵ Other mechanisms of alectinib resistance include EGFR activation as bypass signals,²⁷ coactivation of c-Src and MET,²⁸ and activation of the HGF/MET pathway.¹⁸ A combination therapy of c-Src and MET inhibitors (i.e., saracatinib and crizotinib) is expected for the coactivation of c-Src and MET.²⁸ As for the HGF/MET activation, crizotinib affects resistant tumors via its pathway,^{18,19} and patients with a treatment response reported in this study may have had such

tumors. Further, the next-generation sequencing (NGS) panel tests will be important in clinical practice if treatment strategies for alectinib-resistant tumors are established stratified by each type of resistant mechanisms. Our future study aims to elucidate the relationship between resistance to alectinib and the mechanisms of crizotinib action through biomarker analysis of treatment responders.

In contrast to the ORR, the median PFS associated with crizotinib monotherapy in this study was shorter than that associated with other ALK-TKIs in the alectinib-refractory setting (Table 6). This finding may be explained by the fact that, irrespective of treatment regimens, patients included in this study possessed (by chance) rapidly progressing tumors; the duration of prior treatment with alectinib among patients in our series was shorter than that of other reports (median, 6.7 [range: 12.4–34.1] months) (Table 6).⁵ The reason why the patients enrolled in the study had rapidly progressing tumors may be due to the fact that this study was started immediately after the approval of alectinib as first-line therapy, and therefore many patients with early alectinib resistance were enrolled. Regarding the safety profile, although AEs resulted in treatment discontinuation in one patient (11%), these complications were temporary and manageable with supportive care. Furthermore, all patients were able to receive sequential chemotherapy after the study treatment, retaining favorable general conditions (Table 5). Overall, these findings suggest that treatment with crizotinib in this setting was tolerable.

This study has some limitations. First, the issue of sample size should be raised. With the limited existing preclinical and clinical data of HGF/MET pathway activation in alectinib-resistant tumors, and our decision to place the importance on a clinically meaningful response rate, we set the expected response rate as 50% which led to a very small sample size. Thus this study should be positioned as a first exploratory step to further evaluate and confirm the efficacy of this treatment regimen, and our results are simply hypothesis-generating. Second, when selecting our target population, we did not consider different mechanisms of alectinib resistance. This was also a limitation of previous studies evaluating ceritinib, lorlatinib, and brigatinib (Table 6); the reported efficacy of each drug was limited in each study. Following the successful development of osimertinib for the treatment of secondary T790M-positive tumors among those with relapsed EGFR-mutated NSCLCs,²⁹ future studies should involve biomarker-selected populations of tumors refractory to alectinib.

In summary, treatment with crizotinib following relapse after alectinib therapy in ALK-positive NSCLC patients was associated with moderate efficacy and manageable AEs. Although our study did not meet its predefined efficacy criteria, it offers potential study implications towards future studies and preliminary insight regarding treatment strategies in patients resistant to alectinib.

TABLE 6 Treatment outcomes in alectinib-refractory EML4-ALK-positive NSCLC patients

Reference	Agent	Design	N	Median age (years)	Median treatment duration with prior alectinib (months)	Alectinib only as prior ALK-TKI (%)	ORR (%)	PFS (months)	One-year OS (%)	Comments	Proportion of AEs that led to treatment discontinuation
Hida et al. ²²	Ceritinib	p2	20	51	NA	80	25	3.7	75.6	Prior cytotoxic chemotherapy was allowed.	15%; 3 patients with anemia, acute kidney injury, and pleural effusion.
Solomon et al. ²³	Lorlatinib	p2	28	54	NA	46	32.1	5.5	NA	Analysis of one previous non-crizotinib ALK-TKI cohort. 13 patients had received alectinib.	3%; the most common AE was cognitive effect.
Lin et al. ²⁴	Brigatinib	retro.	22	55	12.4	23	17	4.4	NA	The median usage rate of ALK-TKIs before the trial was two.	5%; grade 3 pneumonitis
This study	Crizotinib	p2	9	63	6.7	78	33.3	2.2	66.7	No previous ALK-TKI, except for alectinib.	11%; grade 4 hepatic dysfunction

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; *EML4*, echinoderm microtubule-associated protein-like 4; N, sample size; NA, not assessed; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; p2, phase 2; PFS, progression-free survival; ref., reference; retro., retrospective; TKI, tyrosine kinase inhibitor.

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CONFLICT OF INTEREST

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REFERENCES

- Isozaki H, Hotta K, Ichihara E, Takigawa N, Ohashi K, Kubo T, et al. Protocol design for the bench to bed trial in alectinib-refractory non-small-cell lung cancer patients harboring the EML4-ALK fusion gene (ALRIGHT/OLCSG1405). *Clin Lung Cancer*. 2016;17:602–5.
- Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isoe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362:2380–8.
- Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368:2385–94.
- Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167–77.

5. Nakagawa K, Hida T, Nokihara H, Morise M, Azuma K, Kim YH, et al. Final progression-free survival results from the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. *Lung Cancer*. 2020;139:195–9.
6. Choi YL, Soda M, Yamashita Y, Ueno T, Takashima J, Nakajima T. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. *N Engl J Med*. 2010;363:1734–9.
7. NCCN Guidelines: Non-Small Cell Lung Cancer, version 2.2020. The National Comprehensive Cancer Network. [cited 2020 Feb 09]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
8. Inoue A, Kobayashi K, Usui K, Maemondo M, Okinaga S, Mikami I, et al. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. *J Clin Oncol*. 2009;27:1394–400.
9. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): An open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:213–22.
10. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2017;378:113–25.
11. Katayama R, Khan TM, Benes C, Lifshits E, Ebi H, Rivera VM, et al. Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. *Proc Natl Acad Sci U S A*. 2011;108:7535–40.
12. Sasaki T, Okuda K, Zheng W, Butrynski J, Capelletti M, Wang L, et al. The neuroblastoma-associated F1174L ALK mutation causes resistance to an ALK kinase inhibitor in ALK-translocated cancers. *Cancer Res*. 2010;70:10038–43.
13. Sasaki T, Koivunen J, Ogino A, Yanagita M, Nikiforow S, Zheng W, et al. A novel ALK secondary mutation and EGFR signaling cause resistance to ALK kinase inhibitors. *Cancer Res*. 2011;71:6051–60.
14. Katayama R, Shaw AT, Khan TM, Mino-Kenudson M, Solomon BJ, Halmos B, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. *Sci Transl Med*. 2012;4:120ra117.
15. Doebele RC, Pilling AB, Aisner DL, Kutateladze TG, Le AT, Weickhardt AJ, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res*. 2012;18:1472–82.
16. Lovly CM, McDonald NT, Chen H, Ortiz-Cuaran S, Heukamp LC, Yan Y, et al. Rationale for co-targeting IGF-1R and ALK in ALK fusion-positive lung cancer. *Nat Med*. 2014;20:1027–34.
17. Isozaki H, Yasugi M, Takigawa N, Hotta K, Ichihara E, Taniguchi A, et al. A new human lung adenocarcinoma cell line harboring the EML4-ALK fusion gene. *Jpn J Clin Oncol*. 2014;44:963–8.
18. Isozaki H, Ichihara E, Takigawa N, Ohashi K, Ochi N, Yasugi M, et al. Non-small cell lung cancer cells acquire resistance to the ALK inhibitor alectinib by activating alternative receptor tyrosine kinases. *Cancer Res*. 2016;76:1506–16.
19. Gouji T, Takashi S, Mitsuhiro T, Yukito I. Crizotinib can overcome acquired resistance to CH5424802: Is amplification of the MET gene a key factor? *J Thorac Oncol*. 2014;9:e27–8.
20. Feng Y, Minca EC, Lanigan C, Liu A, Zhang W, Yin L, et al. High MET receptor expression but not gene amplification in ALK 2p23 rearrangement positive non-small-cell lung cancer. *J Thorac Oncol*. 2014;9:646–53.
21. Scagliotti G, Kim DW, Shaw AT, Ou SH, Riely GJ, Gettinger SN, et al. A large retrospective analysis of the activity of pemetrexed (PEM) in patients (pts) with ALK-positive (ALK+) non-small cell lung cancer (NSCLC) prior to crizotinib (CRIZ). *J Clin Oncol*. 2012;28:7599.
22. Hida T, Seto T, Horinouchi H, Maemondo M, Takeda M, Hotta K, et al. Phase II study of ceritinib in alectinib-pretreated patients with anaplastic lymphoma kinase-rearranged metastatic non-small-cell lung cancer in Japan: ASCEND-9. *Cancer Sci*. 2018;109:2863–72.
23. Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. *Lancet Oncol*. 2018;19:1654–67.
24. Lin JJ, Zhu VW, Schoenfeld AJ, Yeap BY, Saxena A, Ferris LA, et al. Brigatinib in patients with alectinib-refractory ALK-positive NSCLC. *J Thorac Oncol*. 2018;13:1530–8.
25. Gainor JF, Dardaei L, Yoda S, Friboulet L, Leshchiner I, Katayama R, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov*. 2016;6:1118–33.
26. Yanagitani N, Uchibori K, Koike S, Tsukahara M, Kitazono S, Yoshizawa T, et al. Drug resistance mechanisms in Japanese anaplastic lymphoma kinase-positive non-small cell lung cancer and the clinical responses based on the resistant mechanisms. *Cancer Sci*. 2020;111:932–9.
27. Arai S, Takeuchi S, Fukuda K, Taniguchi H, Nishiyama A, Tanimoto A, et al. Osimertinib overcomes alectinib resistance caused by amphiregulin in a leptomeningeal carcinomatosis model of ALK-rearranged lung cancer. *J Thorac Oncol*. 2020;15:752–65.
28. Tsuji T, Ozasa H, Aoki W, Aburaya S, Funazo T, Furugaki K, et al. Alectinib resistance in ALK-rearranged lung cancer by dual salvage signaling in a clinically paired resistance model. *Mol Cancer Res*. 2019;17:212–24.
29. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629–40.

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