

Treatment After Crizotinib Resistance in ALK+ Non-Small-Cell Lung Cancer

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ABSTRACT

Systemic chemotherapy, genotype-based targeted therapies and immunotherapy are widely used in the treatment of advanced non-small-cell lung cancer (NSCLC). Among the targeted therapies, the agents targeting the epidermal growth factor receptor (EGFR), the echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) rearrangement and C-ros oncogene 1 (ROS-1) have currently become standard treatment for cases presenting such molecular anomalies. Of them, cases with ALK-rearrangement displayed dramatic results with a first generation ALK-inhibitor crizotinib; however, most of the patients develop a resistance in a few years. Especially the central nervous system relapses pose the most common clinical problem. Next generation ALK-inhibitors are promising with a high level of effectiveness in this resistance, in which various molecular mechanisms take part. Also, it gains increasing importance to re-perform a biopsy in the progression stage and reveal the mechanisms causing the secondary resistance in those patients.

Keywords: Non-small-cell lung cancer, ALK, Crizotinib, Resistance

ÖZET

ALK-Pozitif Küçük Hücreli Dışı Akciğer Kanseri Crizotinib Direnci Sonrası Tedavi

İleri evre küçük hücreli dışı akciğer kanseri (KHDAK)'nin tedavisinde sistemik kemoterapi, genotipe dayalı hedef tedaviler ve immunoterapi yaygın olarak kullanılmaktadır. Hedef tedaviler arasında epidermal growth factor receptor (EGFR), the echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) rearrangement ve C-ros oncogene 1 (ROS-1)'i hedefleyen ajanlar, bugün için bu moleküler anomalilere sahip hastalarda standard tedavi haline gelmiştir. Bunlardan ALK-rearrangement'i olan hastalarda birinci jenerasyon ALK-inhibitörü crizotinib ile dramatik sonuçlar elde edilmiş olmakla birlikte hastaların çoğunda birkaç yıl içinde direnç gelişmektedir. Özellikle santral sinir sistemi relapsları en sık karşılaşılan klinik sorun olarak karşımıza çıkmaktadır. Çeşitli moleküler mekanizmaların rol oynadığı bu direnç durumunda yeni jenerasyon ALK-inhibitörleri yüksek etkinlikleri ile ümit vadetmektedir. Ayrıca bu hastalarda progresyon aşamasında tekrar biyopsi yapılması ve sekonder dirence neden olan mekanizmaların ortaya konması giderek önem kazanmaktadır.

Anahtar Kelimeler: Küçük hücreli dışı akciğer kanseri, ALK, Crizotinib, Direnç

INTRODUCTION

Lung cancer is the primary cause of cancer-related death worldwide, causing approximately 1.5 million deaths every year.¹ Non-small-cell lung cancer (NSCLC) cases comprise approximately around 85% of all lung cancers. More than half of the NSCLC cases are advanced-stage at the time of diagnosis, and those patients' 5-year survival rate is around 4%.² In the advanced-stage disease, histology-based systemic chemotherapy and genotype-based targeted therapies comprise the main treatment approaches. Today, among the genotype-based targeted therapies, specific tyrosine kinase inhibitors (TKI), erlotinib, gefitinib and afatinib that target the Epidermal Growth Factor Receptor (EGFR); and crizotinib that targets the echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) rearrangement and C-ros oncogene 1 (ROS-1) are widely applied to patients with sensitive molecular anomalies.³⁻⁵ Recently, positive results achieved in the field of immunotherapy have led to a growing number of treatment options.

ALK rearrangement is an oncogenic molecular anomaly observed in 2-7% of patients with NSCLC, and it is presented largely by young patients with a solid-pattern-dominant adenocarcinoma histology and without smoking history.^{6,7} Studies conducted with crizotinib, which inhibits the mesenchymal-epithelial transition factor (MET) and ROS1 alongside ALK, reported significant response rates and survival advantage both in the first line treatment and in patients who received prior treatment. Upon these developments, crizotinib became a primary treatment option widely applied to ALK+ positive patients. Although dramatic results have been achieved with crizotinib, median progression-free survival (PFS) do not exceed 10-12 months, that is, patients present an acquired resistance after a while.³⁻⁵ In this stage, especially the central nervous system (CNS) relapses pose the most common clinical problem. Numerous genetic mutations have been identified as resistance mechanisms to crizotinib, and specific inhibitors are being developed against them. The aim of this review is to evaluate the resistance mechanisms to crizotinib in ALK+ advanced-stage NSCLC and review the potential next generation agents studied to overcome this resistance.

Clinical Results of Crizotinib:

Crizotinib (PF-02341066) is a small oral molecule that was developed as a MET inhibitor at first. However, its ability to inhibit ALK and ROS-1 was discovered later. A phase I (PROFILE 1001)⁸ and a phase II study (PROFILE 1005)⁹, conducted following the promising preclinical findings, calculated the overall response rate (ORR) to be around 60% and median PFS as 9 months. With those results, crizotinib received an accelerated approval from the Food and Drug Administration (FDA) in 2011.

Two phase III studies were conducted to examine the effectiveness of crizotinib on ALK + patients with NSCLC. In the PROFILE 1007¹⁰ study, 347 ALK+ NSCLC patients with a history of platinum-based chemotherapy were randomized into crizotinib vs. docetaxel or pemetrexed arms as the second line treatment. The findings showed that crizotinib was significantly superior to chemotherapy in terms of both ORR (65% vs. 20%, $p < 0.001$) and median PFS (7.7 months vs. 3.0 months, HR: 0.49). The PROFILE 1014¹¹, another phase III study, compared crizotinib with platinum-based combined chemotherapy as the first line treatment. That study evaluated a total of 343 ALK+ patients with NSCLC, and the patients were randomized into crizotinib vs. platinum/pemetrexed combination arms as the first line treatment. The findings again showed that crizotinib was superior to chemotherapy in terms of both ORR (74% vs. 45%, $p < 0.001$) and median PFS (10.9 months vs. 7.0 months, HR: 0.45). Crizotinib is generally well-tolerated, with reported main side effects including vision disorders, diarrhea, edema, high aminotransferase, and neutropenia (Table 1).

Although dramatic response rates and significantly prolonged progression-free survival rates are achieved with crizotinib, resistance is inevitable after a while. The phenomenon of progression, which emerges in 10-12 months following the start of treatment, is manifested as relapses involving multiple sites, particularly the central nervous system. Nevertheless, it may also manifest as oligoprogression in a small group of patients, which refers to progression in a limited number of sites.

Table 1. Completed clinical trials on Crizotinib, a first-generation ALK-inhibitor

Agent	Researcher	Phase	Design	ORR (%)	Median PFS (month)
Crizotinib	Camidge et al ⁸ (PROFILE 1001)	I	On different lines	61	9.7
	Kim et al ⁹ (PROFILE 1005)	II	Cases progressed after ≥1 line of chemotherapy	53	8.5
	Shaw et al ¹⁰ (PROFILE 1007)	III	Crizotinib vs. Chemotherapy in the second line treatment (Pemetrexed or Docetaxel)	65 vs 20	7.7 vs 3.0
	Solomon et al ¹¹ (PROFILE 1014)	III	Crizotinib vs. Platinum+Pemetrexed in the first line treatment	74 vs 45	10.9 vs 7.0

RESISTANCE MECHANISMS to CRIZOTINIB

Two primary mechanisms are reported to take part in the secondary resistance to crizotinib: secondary mutations in the EML4-ALK gene and the activation of alternative bypass signaling pathways.

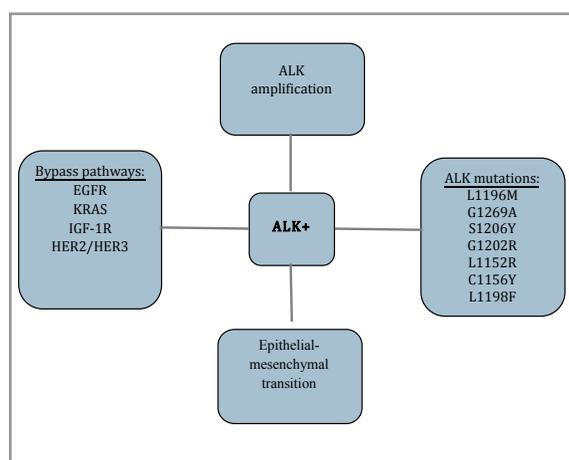


Figure 1. The molecular mechanisms of resistance to crizotinib

Secondary Resistance Mutations in ALK:

Secondary mutations in the ALK gene comprise approximately one-third of the causes of resistance. In this sense, the most frequently observed secondary mutation is L1196M; it arises with the addition of bulky residues to the adenosine triphosphate (ATP)-binding domain site, similar to the EGFR T790M gatekeeper mutation. Other mutations are identified as C1156Y, G1269A, F1174,

L1152R, S1206Y, G1202R, and D1203N.^{3,5,12-15} The second generation ALK-inhibitors play a major role in those secondary mutations, which are the primary cause of resistance in cases progressed under crizotinib therapy (Table 2 and 3) (Figure 1).

ALK Gene Copy Number Changes:

An increased number of ALK fusion gene copies is a major reason for the secondary resistance and accounts for around 20% of the resistance mechanisms. This change may be observed alone or in combination with other secondary resistance mechanisms.^{16,17} However, it is reported that alterations in the number of gene copies play a relatively minor role in resistance due to the potent effects of next generation ALK-inhibitors³ (Figure 1).

Bypass Pathways:

The activation of alternative pathways occupies an important place among the resistance mechanisms to crizotinib. EGFR15 is the most common bypass escape mechanism among these bypass pathways stimulating proliferation independently of ALK, followed by insulin-like growth factor-1 receptor (IGF-1), cKIT, HER2/HER3, and SRC.^{3,15,18-21} Apart from them, the mTOR activation is also reported to induce resistance crizotinib by increasing autophagia in the ALK receptor (Figure 1).⁵

Epithelial-Mesenchymal Transition:

In the epithelial-mesenchymal transition (EMT), tumor cells display a transition from epithelial properties to sarcomatoid properties, thus gaining a

Table 2. Completed clinical trials on next generation ALK-inhibitors

Agent	Researcher	Phase	Design	ORR (%)	Median PFS (month)
Ceritinib	Kim et al ³¹ (ASCEND 1)	I	Cases with a prior history of Chemotherapy, with or without Crizotinib	58	8.2
	Mok et al ³² (ASCEND 2)	II	Patients with a history of Crizotinib	54	5.7
	Felip et al ³³ (ASCEND 3)	II	Patients without a history of ALK-inhibitor	63.7	11.1
	Scagliotti et al ⁵⁰ (ASCEND 5)	III	Ceritinib vs. Chemotherapy in cases progressed under Crizotinib	39 vs 7	5.4 vs 1.6
Alectinib	Ou et al ³⁴	II	Patients with a history of Crizotinib	50	8.9
	Shaw et al ³⁵	II	Patients with a history of Crizotinib	48	8.1
	Nokihara et al ³⁷ (J-ALEX)	III	Alectinib vs. Crizotinib in the first line treatment		Not reached vs 10.2
Brigatinib	Camidge et al ³⁹	I/II	Cases with advanced-stage cancer, including those with ALK+NSCLC	72	12.8
Lorlatinib	Shaw et al ⁴³	I	ALK+ and ROS-1+ NSCLC cases with a history of ALK-inhibitor	40	NR

potential for further spreading and causing an invasion. The EMT rate is not clear in the lung cancer but it is suggested that EMT markers are expressed at a higher rate in ALK+ patients.²² Kobayashi et al.²³ reported a reduced expression of epithelial markers and increased sarcomatoid changes at the progression stage in a patient. Some suggest that this resistance mechanism may play a role in the developed resistance to both crizotinib and next generation ALK-inhibitors (Figure 1).³

Despite all those mechanisms, the resistance mechanism remains unknown in approximately 25% of the cases. Therefore, it is of great importance to re-perform a biopsy to reveal resistance mechanisms at the progression stage.

APPROACHES to OVERCOMING CRIZOTINIB RESISTANCE

Influence of the Progression Type on the Clinical Decision:

Before deciding on a new treatment option for a patient progressed during the ALK-TKI treatment, it is useful to identify the type of progression.^{3,24} In this sense, two types of progression have been described: oligoprogression and systemic progression. In oligoprogression, the primary tumor is under control, the disease progresses slowly and includes a limited number of intracranial or extracranial asymptomatic metastases. Usually, the

lesions with a limited progression are subjected to a stereotactic ablative radiotherapy and TKI treatment is maintained, which is considered a proper approach in such cases.²⁵ In systemic progression, however, other treatment alternatives are recommended, systemic treatment in particular.

Since crizotinib has a limited transition to the CNS, the cases progressed under crizotinib therapy frequently display brain metastases. This is due to the pharmacokinetic properties of crizotinib; it has a low effectiveness in the CNS as it is a substrate for the p-glycoprotein, which is an efflux pump that prevents the accumulation of drugs in the CNS.²⁶ In a phase I study called PROFILE 1001, 10 patients with CSN metastasis underwent local radiotherapy and continued to receive crizotinib, those patients were reported to receive it without progression between 82 and 591 days.²⁷ A combined analysis of PROFILE 1005 and 1007 studies evaluated 275 cases with asymptomatic brain metastasis. As part of the analysis, in which 166 of the cases were reported to have received chemotherapy before while 109 of them did not, the intracranial DCR was measured as 62% and 52% at week 12 and the time until intracranial disease progression was 13 months and 7 months, respectively.²⁸

In cases developing a limited number of extracranial metastases under crizotinib therapy, clinicians sometimes prefer to apply local ablative therapy to those sites and continue crizotinib. This approach

is based on a rationale that there are crizotinib-resistant clones in sites presenting limited progression; as part of a related study including 14 ALK+ NSCLC cases, clinicians continued to administer crizotinib following a local ablative therapy and secured an extra PFS advantage of 7 months.²⁹ Therefore, in addition to a transition to the next generation ALK-inhibitors, to continue crizotinib following a local ablative therapy seems to be a proper option both in CNS-metastatic cases and the cases with oligometastatic extracranial metastasis.

Next Generation ALK-inhibitors:

Next generation ALK-inhibitors draw attention with their high effectiveness in cases progressed under crizotinib. Ceritinib, alectinib, brigatinib, and lorlatinib are among the primary next generation ALK-inhibitors developed in this context.

Ceritinib:

Ceritinib (LDK378) is an oral, ATP-competitive and selective ALK-inhibitor, it is 20 times more potent than crizotinib.³⁰ As part of ASCEND-1, a phase I study, 146 ALK+ cases were administered crizotinib at a dose of 750 mg/day. 163 of them had a history of crizotinib and the remaining 83 were crizotinib-naïve; the study found ORR as 53% and 66%, respectively. Median PFS was found 8.2 months in the whole group, which remained at 6.9 months for the group of cases with a crizotinib history.³¹ Both FDA and EMA approvals were obtained with these results. As part of the ASCEND-2, a phase II study conducted subsequently, 140 patients with a history of crizotinib or chemotherapy were administered crizotinib at a dose of 750 mg/day. Consequently, the ORR was 38.6%, disease control rate (DCR) was 77.1%, and median PFS was 5.7 months.³² However, the ASCEND-3 study including 124 patients who did not receive ALK-inhibitor before found the ORR as 63%, DCR as 89.5%, and median PFS as 11.1 months (Table 2).³³

Ceritinib is highly effective in CNS metastases as well. Among the cases without a history of ALK-inhibitor as part of ASCEND-2 and ASCEND-3 studies, no significant difference was detected be-

tween the cases with intracranial disease and those with extracranial metastasis in terms ORR and PFS.^{32,33}

Alectinib:

Alectinib (CH5424802) is a potent second generation ALK-inhibitor. In addition to being effective in numerous mutations that play a role in crizotinib resistance, it is also an ROS-1 inhibitor. Two phase II studies examined the effectiveness of alectinib in the second line treatment. As part of the first one, 138 crizotinib-resistant cases were administered alectinib at a dose of 1200 mg/day, and the ORR was 50%, DCR was 69%, and median PFS was 8.9 months.³⁴ Likewise, in the second phase II study, 87 crizotinib-resistant cases were administered alectinib at a dose of 1200 mg/day; the ORR was 48% and median PFS was 8.1 months.³⁵ It obtained FDA approval with this finding.

Alectinib's effectiveness in the first line treatment has been investigated as well. As part of AF-001JP, a phase II study, ALK+ cases received alectinib as the first line treatment with 93.4% response rate and a median PFS of 29 months.³⁶ A subsequent phase III study (J-ALEX) including Japanese patients randomized ALK+ cases into crizotinib vs. alectinib arms as the first line treatment. Consequently, alectinib was found superior to crizotinib in terms of median PFS (not reached vs. 10.2 months). This superiority was reported to be applicable to all subgroups (Table 2).³⁷ We are currently waiting for the findings of Global ALEX study, which features a similar design.

Alectinib also has a high level of effectiveness in the CNS metastases. The phase II studies conducted on crizotinib-resistant cases report CNS disease control rates between 83% and 89%.³⁶ The CNS metastasis is the primary one; a complete response was achieved in 43% of the patients who had not received radiotherapy. Similarly, it was shown by J-ALEX study to display a higher effectiveness than crizotinib in cases with brain metastasis (HR: 0.08).³⁷ Alectinib's not being a substrate of the glycoprotein efflux pump is considered the most important reason for its high effectiveness in the CNS metastases.³⁸

Brigatinib:

Brigatinib (AP26113) is a small molecule TKI, it inhibits ALK – including resistant ALK mutations –, ROS-1, and EGFR, including T790M. A phase I/II study conducted on ALK+ NSCLC patients found ORR as 69% and 100% in patients with and without a history of crizotinib, respectively. Likewise, median PFS was 56 weeks for the whole group, while it decreased to 47 weeks among those who had received crizotinib.³⁹ Brigatinib has a high rate of crossing blood-brain barrier as well. In a retrospective analysis of 15 CNS-metastatic patients treated with brigatinib, intracranial response rate and disease control rate was found 53% and 86%, respectively (Table 2).⁴⁰

Lorlatinib:

Lorlatinib (PF-063922) is a small molecule TKI that is able to inhibit both ALK and ROS-1 with a high capacity of brain penetration.^{41,42} Especially its high effectiveness on the G1202R mutation in comparison to other agents is one of its major advantages. Alongside the fact that a phase I study demonstrated its high effectiveness in patients who had received ALK-inhibitor⁴³, it is suggested that the observations indicating the re-occurrence of crizotinib sensitivity in patients progressed after lorlatinib bring a new dimension to the struggle against resistance (Table 2).⁴⁴

Other ALK-inhibitors:

There are ongoing early phase studies on other next generation ALK-inhibitors such as ASP3026⁴⁵, X-396⁴⁶, TSR-011⁴⁷, entrectinib⁴⁸ and CEP-28122⁴⁹, as well as basket studies including a variety of malignancies.

Other Approaches:

- Chemotherapy:

One of the most important problems concerning treatment preferences for the patients progressed under crizotinib is to decide whether to choose widely-administered chemotherapy or next generation ALK-inhibitors. As part of the ASCEND-5 study conducted on this matter, 231 ALK+ NSCLC

patients progressed under crizotinib were randomized into Ceritinib or Chemotherapy (Pemetrexed or Docetaxel) arms. According to the findings, Ceritinib was found superior in terms of ORR (39% vs 7%) and median PFS (5.4 months vs 1.6 months). No difference was detected in the overall survival due to the crossover after progression.⁵⁰

- Immunotherapy:

Immunotherapy is another treatment alternative after a patient develops resistance to crizotinib. Regarding immunotherapy, which has recently drawn a great deal of attention, a series of studies have been conducted with various immune checkpoint inhibitors in the advanced-stage disease and remarkable findings have been achieved. In this sense, especially nivolumab, pembrolizumab and atezolizumab, which are inhibitors developed against the programmed death receptor-1 (PD-1) and its ligand, i.e. programmed death ligand-1 (PD-L1), obtained FDA approval and found their way into treatment guidelines thanks to their high effectiveness.⁵¹⁻⁵³

The Approach After Progression under Crizotinib:

Today, the most rational approach for the patients progressed under crizotinib seems to shift to the next generation ALK-inhibitors. However, since the transition to the CNS is limited, an alternative approach for patients presenting only a CNS progression may be to administer a local therapy such as radiotherapy and maintain Crizotinib. Chemotherapy does not seem to be a first preference due to its low effectiveness compared to the next generation ALK-inhibitors. Today, the subsequent administration of ALK-inhibitors is suggested to offer the best survival outcome, with median PFS and median OS reaching 17.4 and 49.4 months, respectively.⁵⁴ On the other hand, it is still an important and pending question as to which one to be used among the next generation ALK-inhibitors. As there is no study comparing the next generation ALK-inhibitors with each other, and since each one acts on different mutations, one should ideally perform a re-biopsy during the progression stage and reveal the resistance pattern in order to pick up

Table 3. Effectiveness of next generation ALK-inhibitors in crizotinib-resistant ALK mutations

	L1196M	G1269A/S	C1156Y	R1275Q	L1198F	S1206Y	I1171T	V1180L	F1174V/L	D1203N	G1202R
Crizotinib ⁸⁻¹⁰	--	--	--	--	+	--	+	+	--	--	--
Ceritinib ³¹⁻³³	+	+	--	+	--	+	+	+	--	--	--
Alectinib ^{34,35}	+	+	+	+	--	+	--	--	+	+	--
Brigatinib ³⁹	+	+			--		+	+	+		+
Lorlatinib ⁴³	+	+	+		--	+			+		+

a relevant agent⁵ (Table 3). Nevertheless, re-biopsy sometimes becomes impossible due to the location of the primary tumor or patient's refusal. In such a case, molecular analyses may be performed based on the circulating tumor cell DNA (ctDNA) through a liquid biopsy.⁵⁰ As the patients may potentially develop a resistance to the next generation ALK-inhibitors after a while, it is required to carry out repetitive tissue/liquid biopsies when progression takes place after each treatment.

In conclusion, crizotinib, a first generation ALK-inhibitor, has long been the standard and routine approach for the advanced-stage NSCLC patients with ALK-rearrangement. Nevertheless, as the secondary resistance and hence progression becomes inevitable after a while, the principles of approach should be better established. Today, next generation ALK-inhibitors appear to be the best approach thanks to their high specific effectiveness and low toxicity profiles. Besides, shifting to immunotherapy and approaches for other pathways are other alternative options. Further clarification of the molecular patterns of the secondary resistance patterns will enable more specific treatments in the future.

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