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Review

Anaplastic Lymphoma Kinase Fusion:
A Review of Therapeutic Drugs and Treatment Strategies

Go Makimoto[a,b]*[§], Kadoaki Ohashi[c], Yoshinobu Maeda[b], and Katsuyuki Kiura[c]

[a]*Department of Respiratory Medicine, National Hospital Organization Iwakuni Clinical Center, Iwakuni, Yamaguchi 740-8510, Japan, [b]Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, [c]Department of Respiratory Medicine, Okayama University Hospital, Okayama 700-8558, Japan*

The prognosis of advanced non-small cell lung cancer (NSCLC) patients has improved in recent decades, especially for patients with an oncogenic driver mutation. Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) are effective for patients with the *echinoderm microtubule-associated protein-like 4-ALK* fusion gene. Several ALK-TKIs have been established: the first-generation ALK-TKI, crizotinib; second-generation ALK-TKIs, alectinib and ceritinib; and third-generation ALK-TKI, lorlatinib. Some ALK-TKIs are effective for tumors that are resistant to other ALK-TKIs; however, as is known in epidermal growth factor receptor-mutant lung cancer, tumor resistance is inevitable. *ALK*-positive NSCLCs acquire resistance via various mechanisms, making it a heterogeneous disease. Therefore, it is necessary to develop next-generation treatment strategies, such as the use of next-generation ALK-TKIs for secondary mutations, or combination therapies with ALK-TKIs and other TKIs. In this review, we summarize the development and use of ALK-TKIs, prior pivotal clinical trials, and resistance mechanisms.

Key words: lung cancer, anaplastic lymphoma kinase, tyrosine kinase inhibitors, resistance mechanism

T he *anaplastic lymphoma kinase (ALK)* gene is located on chromosome 2p23 and expressed in fetal neural cells. The *ALK* gene is phosphorylated and activated to control cell proliferation, survival, and differentiation during the development of the nervous system [1]. ALK t(2 ; 5) chromosomal translocation was first reported in anaplastic large cell lymphomas (ALCLs) in 1994 [2]. ALCL, also known as Ki-1 lymphoma or large-cell anaplastic lymphoma, is a subtype of human non-Hodgkin's lymphoma that is characterized by the expression of CD30 (Ki-1 antigen) and a peculiar large anaplastic morphology that mimics Reed-Sternberg cells [3,4]. The t(2 ; 5)(p23 ; q35)

chromosomal translocation, which forms the nucleophosmin (NPM)-ALK chimeric protein (p80[NPM/ALK]), was first reported in Japan [5,6] and the United States [7]. Shiota *et al*. also report that p80-positive ALCL is a distinct entity both clinically and pathogenetically and should be differentiated from p80-negative ALCL [8]. Subsequently, more than 25 patterns of *ALK* fusion partners have been reported [9,10]. In 2007 in Japan, the *echinoderm microtubule-associated protein-like 4 (EML4)- ALK* fusion gene was found to cause lung cancer [11]. This gene has been discovered in about 3-5% of non-small cell lung cancer (NSCLC) patients [12]. ALK tyrosine kinase is automatically activated by multimerization with fusion partners, causing cancers through the overexpression of cell proliferation signals.

Hence, a blockade of ALK tyrosine kinase activation significantly inhibits cell proliferation in *ALK* fusion gene-positive cancer. Subsequently, several ALK tyrosine kinase inhibitors (TKIs) have been developed and evaluated for efficacy in pivotal EML4-ALK-positive NSCLC clinical trials. A total of four ALK-TKIs are currently approved in Japan: the first-generation ALK-TKI crizotinib; second-generation ALK-TKIs alectinib and ceritinib; and third-generation ALK-TKI lorlatinib. Notably, the second-generation ALK-TKI alectinib showed a high objective response rate (93.5%) and long progression-free survival (3-year progression-free survival rate: 62%) for *ALK*-positive NSCLC [13]. In addition, alectinib is associated with fewer severe adverse effects such as diarrhea and nausea than crizotinib (described below) [14,15]. Thus, alectinib is widely used as the first-line treatment in *ALK*-positive lung cancer patients. However, acquired resistance is inevitable, and is an important clinical issue. In this review, we summarize the development of ALK-TKIs, prior pivotal clinical trials, and mechanisms of resistance to ALK-TKIs.

The Development of ALK-TKIs and Results of Pivotal Clinical Trials

Crizotinib. Crizotinib was the first molecular-targeted drug approved for *EML4-ALK* fusion-positive NSCLC. It was approved in 2012 based on the PROFILE 1007 study, a randomized phase 3 trial comparing crizotinib with standard cytotoxic chemotherapy (pemetrexed or docetaxel) in patients with locally advanced or metastatic *ALK*-positive lung cancer who had previously received one platinum-based regimen [16]. Patients were randomly assigned to the crizotinib arm (n = 173) or the standard chemotherapy arm (n = 174: pemetrexed 58%, docetaxel 42%). The primary endpoint was median progression-free survival (mPFS), which was 7.7 months in the crizotinib arm and 3.0 months in the chemotherapy arm (hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.37-0.64; $p < 0.001$). Subsequently, in 2014, a phase 3 trial comparing the mPFS with crizotinib in cytotoxic chemotherapy as the first-line therapy in patients with advanced *ALK*-positive NSCLC (PROFILE1014) was reported (Table 1) [17,18]. In the PROFILE1014 study, the primary endpoint was mPFS, which was 10.9 months in the crizotinib arm and 7.0 months in the chemotherapy arm (HR 0.45; 95% CI, 0.35-0.60; $p < 0.001$). Based on this result, crizotinib was approved as the first-line treatment for *ALK*-positive advanced NSCLC. Although crizotinib was the first approved drug for treating *ALK*-positive NSCLC, it has some limitations with regard to its safety profile *i.e.*, it causes visual impairment, diarrhea, vomiting, and liver damage. Adverse effects arise because crizotinib inhibits not only ALK but also other kinases such as *MET proto-oncogene, receptor tyrosine kinase (MET)*, and *c-ROS oncogene 1 (ROS1)*. Crizotinib has been approved for *ROS1* fusion gene-positive NSCLCs [19,20].

Alectinib. The second-generation ALK-TKI alectinib was first approved in Japan in 2014. First, two phase 1/2 trials were conducted: the AF-001JP trial for crizotinib-untreated patients, and the AF-002JG trial for crizotinib-resistant patients (Table 2). Although these trials were single-arm studies, alectinib showed an unprecedented high response rate (93.5%), a long mPFS (not reached), and a high 3-year PFS rate (62%) in the AF-001JP trial [13,21], and a high response rate (55%) in the AF-002JG trial [22]. Based on these promising results, two phase 2 trials were conducted to investigate the anti-tumor activity of alectinib for crizotinib-resistant *ALK*-positive NSCLCs. Ou *et al.* report that the response rate was 50% (95%CI, 41-59%) and the mPFS was 8.9 months (95%CI, 5.6-11.3 months)

Table 1 Prior pivotal randomized phase 3 clinical trials on ALK-positive non-small-cell lung cancer (NSCLC) (ALK-TKI naïve)

Study name	Ref.	ALK-TKI	Comparative arm	Treatment line	Patients (n)	mPFS (months)	PFS HR [95% CI]	mOS (months)	OS HR [95% CI]
PROFILE1014	[17,18]	Crizotinib	Chemotherapy	Naïve	172	10.9 vs 7.0	0.45 [0.35−0.60]	NR vs 47.5	0.346 [0.081−0.718]
J-ALEX	[14,25]	Alectinib	Crizotinib	ALK-TKI naïve	103	34.1 vs 10.2	0.37 [0.26−0.52]	NR vs 43.7	0.80 [0.35−1.82]*
ALEX	[15,26]	Alectinib	Crizotinib	Naïve	152	34.8 vs 10.9	0.43 [0.32−0.58]	NR vs NR	0.76 [0.50−1.15]
ASCEND-4	[30]	Ceritinib	Chemotherapy	Naïve	189	16.6 vs 8.1	0.55 [0.42−0.73]	NR vs 26.2	0.73 [0.50−1.08]
ALTA-1L	[36]	Brigatinib	Crizotinib	ALK-TKI naïve	137	NR vs 9.8	0.49 [0.33−0.74]	NR vs NR	0.98 [0.50−1.93]

ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; mPFS, median progression-free survival; HR, hazard ratio; CI, confidence interval; mOS, median overall survival; NR, not reached.
*99.8799% CI

Table 2　Prior pivotal clinical trials on ALK-positive non-small-cell lung cancer (NSCLC) (ALK-TKI pretreated)

Study name	Ref.	First Author	Phase	Prior treatment	ALK-TKI	Patients (n)	ORR (%) [95% CI]	mPFS (months) [95% CI]	mOS (months) [95% CI]
AF002JG	[22]	Gadgeel SM	1/2	Crizotinib	Alectinib	47	55	NA	NA
Alectinib	[23]	Ou SH	2	Crizotinib	Alectinib	138	50 [41–59]	8.9 [5.6–11.3]	NA
Alectinib	[24]	Shaw AT	2	Crizotinib	Alectinib	87	48 [36–60]	8.1 [6.2–12.6]	NA
ASCEND-1	[28]	Kim DW	1	Crizotinib	Ceritinib	163	56.4 [48.5–64.2]	6.9 [5.6–8.7]	16.7 [14.8–NR]
ASCEND-2	[29]	Crino L	2	Platinum doublet Crizotinib	Ceritinib	140	38.6 [30.5–47.2]	5.7 [5.4–7.6]	14.9 [13.5–NR]
ASCEND-5	[31]	Shaw AT	3	Platinum doublet Crizotinib	Ceritinib or PEM/DOC	115 116	39.1 [30.2–48.7] 6.9 [3.0–13.1]	5.4 [4.1–6.9] 1.6 [1.4–2.8]	18.1 [13.4–23.9] 20.1 [11.9–25.1]
ASCEND-9	[32]	Hida T	2	Alectinib ± Crizotinib	Ceritinib	20	25 [8.7–49.1]	3.7 [1.9–5.3]	NA
Lorlatinib	[33]	Shaw AT	1	ALK-TKI	Lorlatinib	41	46 [31–63]	9.6 [3.4–16.6]	NA
Lorlatinib	[34]	Solomon BJ	2			228			
EXP2-3A				Crizotinib	Lorlatinib	59	69.5 [56.1–80.8]	NR [12.5–NR]	NA
EXP3B				Other ALK-TKI	Lorlatinib	28	32.1 [15.9–52.4]	5.5 [2.7–9.0]	NA
EXP4-5				2-3 ALK-TKI	Lorlatinib	111	38.7 [29.6–48.5]	6.9 [5.4–9.5]	NA
ALTA	[35]	Camidge DR	2	Crizotinib	Brigatinib (90) Brigatinib (180)	112 110	40 [29–52] 59 [47–70]	8.8 [5.6–11.1] 12.9 [9.3–NR]	NR [NR–NR] NR [17.8–NR]

ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; ORR, objective response rate; mPFS, median progression free survival; mOS, median overall survival; NR, not reached; PEM, pemetrexed; DOC, docetaxel; NA, not accessed.

[23]. Shaw *et al.* also obtained similar results, reporting a response rate of 48% (95%CI, 36-60%) and mPFS of 8.1 months (95%CI, 6.2-12.6 months) [24]. Subsequently, two randomized phase 3 trials were conducted to compare the mPFS of alectinib with that of crizotinib in ALK inhibitor-naive *ALK*-positive NSCLC patients (Table 1). The first study, the J-ALEX trial, conducted in Japan, showed significant prolongation of mPFS in the alectinib arm (300 mg twice daily) (alectinib for 34.1 months vs. crizotinib for 10.2 months; HR, 0.37; 95%CI, 0.26-0.52; $p < 0.0001$) [14, 25], and the occurrence of grade 3 or 4 adverse events was more frequent with crizotinib (60.6%) than with alectinib (36.9%). Another study, the ALEX trial, was conducted as a global phase 3 study excluding Japan. In this trial, the PFS rate was significantly higher in the alectinib arm (600 mg twice daily) than in the crizotinib arm (1-year event-free survival rate, 68.4% [95%CI, 61.0-75.9] vs. 48.7% [95%CI, 40.4-56.9]; $p < 0.001$), and the mPFS with alectinib was 34.8 months compared to 10.9 months with crizotinib (HR 0.43, 95%CI, 0.32-0.58; $p < 0.001$) [15, 26]. In addition, tumor progression to the central nervous system was less frequent in the alectinib group (12%) compared to the crizotinib group (45%). Consequently, alectinib was recommended as the first-line therapy for *ALK*-positive advanced NSCLCs.

Ceritinib.　　Another second-generation ALK-TKI, ceritinib, was approved in 2016. The ASCEND-1 trial was a phase 1 clinical trial to assess the efficacy of ceri-

tinib in ALK inhibitor-pretreated and ALK inhibitor-naïve NSCLC patients [27, 28]. The overall response rate was 56.4% (95%CI, 48.5-64.2%) in ALK inhibitor-pretreated patients (n = 163) and 72.3% (95%CI, 61.4-81.6%) in ALK inhibitor-naïve patients (n = 83). The median PFS was 6.9 months (95%CI, 5.6-8.7 months) in ALK inhibitor-pretreated patients and 18.4 months (95%CI, 11.1-not reached (NR)) in ALK inhibitor-naïve patients. Next, the ASCEND-2 phase 2 trial was conducted to evaluate efficacy and safety in *ALK*-positive NSCLC patients who had been treated with at least one platinum-based chemotherapy and had experienced tumor progression after crizotinib treatment [29] (Table 2). The overall response rate was 38.6% (95%CI, 30.5-47.2%), and the mPFS was 5.7 months (95%CI, 5.4-7.6 months); therefore, ceritinib was approved for crizotinib-resistant *ALK*-positive NSCLCs. Randomized phase 3 trials were subsequently conducted: the ASCEND-4 and ASCEND-5 trials. The ASCEND-4 trial, which compared first-line ceritinib with platinum-based chemotherapy (cisplatin or carboplatin/pemetrexed), showed that mPFS was 16.6 months (95%CI, 12.6-27.2) in the ceritinib arm and 8.1 months (95%CI, 5.8-11.1) in the chemotherapy arm (HR 0.55, 95%CI, 0.42-0.73; $p < 0.00001$) (Table 1) [30]. After that, ceritinib was approved for ALK inhibitor-naïve NSCLC in 2017. The ASCEND-5 trial, which compared ceritinib with chemotherapy (pemetrexed or docetaxel) in patients who had previously

received chemotherapy and crizotinib, demonstrated that ceritinib yielded a significant improvement in mPFS compared to chemotherapy (5.4 months [95%CI, 4.1-6.9] for ceritinib vs. 1.6 months [95%CI, 1.4-2.8] for chemotherapy; HR 0.49 [0.36-0.67]; $p < 0.0001$) (Table 2) [31]. The ASCEND-9 trial was conducted to examine ceritinib efficacy for alectinib-resistant ALK-positive NSCLC. A total of 20 alectinib-resistant patients were enrolled in this prospective phase 2 study, which found an overall response rate of 25% (95%CI: 8.7-49.1), a disease control rate of 70.0% (95%CI: 45.7-88.1), and mPFS of 3.7 months (95%CI: 1.9-5.3) (Table 2) [32]. No trial has yet compared the effects of ceritinib with those of alectinib. However, ceritinib has more frequent gastrointestinal toxicities than alectinib (the ALEX study), including diarrhea (85% vs. 12%), nausea (80% vs. 14%), and vomiting (65% vs. 7%). Therefore, ceritinib is considered a salvage treatment option for crizotinib- or alectinib-resistant ALK-positive lung cancers.

Lorlatinib.　The third-generation ALK-TKI lorlatinib was developed as a selective and brain-penetrant ALK inhibitor. In a phase 1 study, which was a single-arm, first-in-human dose-escalation study, lorlatinib demonstrated an objective response in 19/41 patients (46%; 95%CI: 31-63) who had received two or more ALK-TKIs [33]. A subsequent global phase 2 study was conducted to evaluate the efficacy of lorlatinib. ALK-positive NSCLC patients were enrolled into different expansions as follows: ALK treatment-naïve (EXP1, n = 30); previously received crizotinib without (EXP2, n = 27) or with (EXP3A; n = 32) chemotherapy; received one previous non-crizotinib ALK-TKI, with or without chemotherapy (EXP3B, n = 28); received two (EXP4, n = 66) or three (EXP5, n = 46) previous ALK-TKIs with or without chemotherapy (Table 2). The primary endpoint was overall and intracranial tumor response. In the EXP1 group, the objective response rate was 27/30 (90.0%; 95%CI, 73.5-97.9), and intracranial responses were observed in 2/3 of patients (66.7%; 95%CI, 9.4-99.2). In the EXP2-5 groups, the objective response rate was 93/198 (47.0%; 95%CI, 39.9-54.2), and intracranial responses were observed in 51/81 patients (63.0%; 95%CI, 51.5-73.4). In the subgroup analysis, the objective response rate was 41/59 (69.5%; 95%CI, 56.1-80.8) in EXP2-3A, 9/28 (32.1%; 95%CI, 15.9-52.4) in EXP3B, and 43/111 (38.7%; 95%CI, 29.6-48.5) in EXP4-5. Objective intracranial

response was achieved in 20/23 patients (87.0%; 95%CI, 66.4-97.2) in EXP2-3A, 5/9 (55.6%; 95%CI, 21.2-86.3) in EXP3B and 26/49 (53.1%; 95% CI, 38.3-67.5) in EXP4-5 [34]. Thus, lorlatinib was approved in 2018 for ALK-TKI-resistant or intolerant ALK-positive NSCLCs. In this trial, relatively unique adverse effects were observed, such as hypercholesterolemia (81%), hypertriglyceridemia (60%) edema (43%), and cognitive defects (18%). A randomized phase 3 study, the CROWN trial (NCT03052608), comparing lorlatinib with crizotinib as a first-line treatment for ALK-positive NSCLC patients, is now recruiting.

Brigatinib.　The approval of brigatinib was accelerated in the United States in April 2017 for the treatment of ALK-positive NSCLC patients who had resistance to or were intolerant to crizotinib. A randomized phase 2 trial, ALTA, was the rationale for this approval (Table 2) [35]. In this study, crizotinib-resistant ALK-positive advanced NSCLC patients were randomly assigned (1 : 1) to receive brigatinib at 90 mg once daily (arm A) or 180 mg once daily with a 7-day lead-in at 90 mg (arm B). The objective response rate, mPFS, and median overall survival were 32/80 (40%; 95%CI, 29-52), 8.8 months (95%CI, 5.6-11.1), and NR (95%CI, NR-NR) in arm A, respectively, and 43/73 (59%; 95%CI, 47-70), 12.9 months (95%CI, 9.3-NR) and NR (95%CI, 17.8-NR) in arm B. In patients with brain metastases, the intracranial objective response rate was 12/26 (46%; 95%CI, 27-67) in arm A, and 12/18 (67%; 95%CI, 41-87) in arm B. Thus, brigatinib yielded substantial intracranial responses in crizotinib-resistant ALK-positive NSCLC. In the first-line setting, the ALTA-1L randomized phase 3 trial was conducted to compare brigatinib with crizotinib for the treatment of ALK inhibitor-naïve ALK-positive NSCLC patients (Table 1) [36]. The mPFS, which was the primary endpoint, was NR in the brigatinib arm and 9.8 months (95%CI, 9.0-12.9) in the crizotinib arm (HR 0.49; 95%CI, 0.33-0.74; $p < 0.001$). In Japan, a single-arm, multicenter, phase 2 study of brigatinib in Japanese patients with ALK-positive NSCLC (NCT03410108) is currently recruiting to evaluate the efficacy of brigatinib.
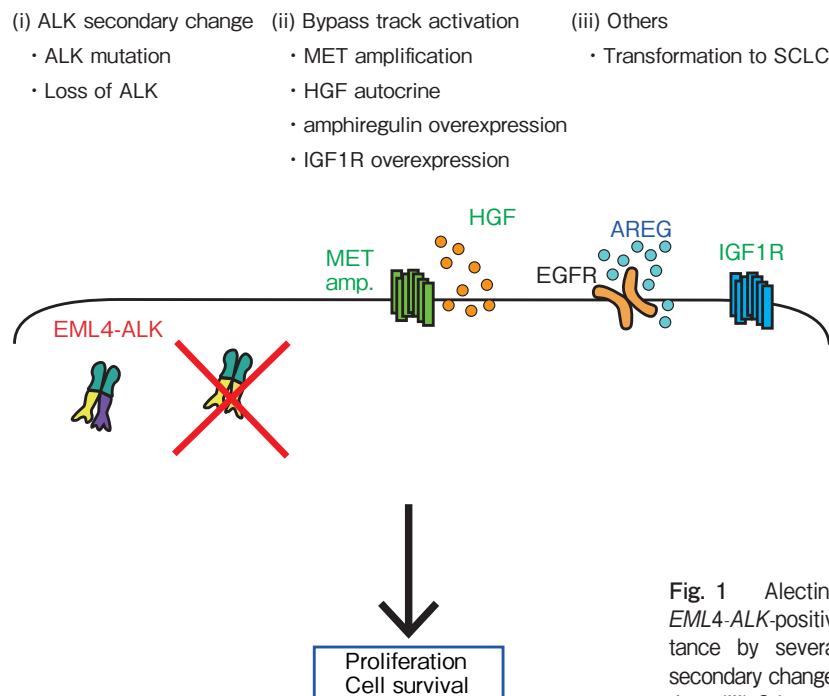
Mechanisms of Drug Resistance to Alectinib

Primary resistance to ALK-TKIs.　Although there have been few reports on primary resistance to alectinib, several cases of primary resistance to crizotinib

have been reported [37], with the following reported primary resistance mechanisms: MYC amplification [38], a new ALK fusion partner (Cap methyltransferase 1-ALK fusion) [39], epidermal growth factor receptor (EGFR) mutation [40,41], KRAS mutation [42] and BIM polymorphism [43]. These primary resistances are relatively rare compared to the secondary resistance discussed below; hence, their precise mechanisms have not yet been clarified.

Secondary resistance to alectinib. As in the case of other molecular-targeted therapies for advanced NSCLC, acquired resistance to ALK-TKI is an inevitable clinical problem. Alectinib is recommended as the first-line therapy for *ALK*-positive advanced NSCLCs; we therefore focus on resistance to alectinib in this section. To date, several mechanisms of resistance to alectinib, such as secondary resistance *ALK* mutations [44-49], bypass track activation via *MET* gene amplification [50,51], MET activation via hepatocyte growth factor autocrine stimulation [52], EGFR ligand amphiregulin overexpression [51], and transformation to small-cell lung cancer [53-55] have been reported in clinical samples (Figure 1). Several types of secondary resistance *ALK* mutations have been reported. Secondary resistance mutations to alectinib, which is widely used as a

first-line TKI treatment for *ALK*-positive NSCLC, include I1171N, G1202R, I1171S, I1171T, and V1180L [48,56]. Of these secondary mutations, all other than G1202R are sensitive to ceritinib or lorlatinib, and the G1202R mutation is sensitive to lorlatinib [57].

After sequential ALK-TKI treatment, compound ALK mutations can occur. Yoda *et al.* report that sequential ALK-TKIs may induce the emergence of compound ALK mutations [58], and several compound mutations have been found, such as L1196M + G1202R and C1156Y + L1198F. In addition, interestingly, the C1156Y mutation is known as a crizotinib-resistant mutation, while the C1156Y + L1198F compound mutation, which occurs after crizotinib-lorlatinib sequential therapy, is sensitive to crizotinib [59]. Okada *et al.* recently reported the sensitivity of ALK inhibitors for compound ALK mutations using *in silico* simulation. In their study, the I1171N + L1256F compound mutation was found to be highly resistant to lorlatinib but more sensitive to alectinib than the I1171N mutation alone. The L1256F mutation was the first highly lorlatinib-resistant single mutation but, interestingly, it is highly sensitive to alectinib [60]. Thus, variations in ALK secondary mutations are very complicated.

(i) ALK secondary change   (ii) Bypass track activation   (iii) Others
  · ALK mutation   · MET amplification   · Transformation to SCLC
  · Loss of ALK   · HGF autocrine
                     · amphiregulin overexpression
                     · IGF1R overexpression

Fig. 1 Alectinib-resistant mechanisms. *EML4-ALK*-positive NSCLCs acquire resistance by several mechanisms: (i) ALK secondary change, (ii) Bypass track activation, (iii) Other mechanisms.

Rapidly acquired resistance to alectinib. Alectinib is considered the standard therapy for patients with NSCLC harboring ALK fusion genes. However, some patients rapidly acquire resistance to alectinib, resulting in highly unfavorable prognoses. The underlying mechanisms for rapid resistance to alectinib remain to be clarified, but we previously reported that a high tumor mutation burden could be a contributing factor [51]. In our previous report, we used next-generation sequencing to analyze *ALK*-positive clinical samples (treatment-naïve samples and autopsy samples) from one patient who developed rapid resistance to alectinib within 3 months. Our comprehensive analysis revealed the heterogeneous tumor evolution of autopsy samples compared to treatment-naïve samples.

Treatment Strategy for ALK-positive Lung Cancer

Based on pivotal clinical studies, mild adverse effects, and a stunning disease control rate, alectinib is often used as the first-line ALK-TKI. Regarding second-line therapy, several sequential ALK-TKI treatment trials have been reported to date (Table 2). Nevertheless, there are limited data on the efficacy of ALK-TKIs after resistance to alectinib has been acquired. Therefore, there is no definite treatment sequence used in ALK-TKI treatment at present.

When resistance is induced by a secondary mutation in the ALK kinase domain, a second- or third-generation ALK-TKI such as ceritinib, brigatinib, or lorlatinib is expected to overcome the resistance. Notably, G1202R, a highly resistant mutation to first- and second-generation ALK-TKIs, is sensitive to the third-generation ALK-TKI lorlatinib. The G1202R mutation is more frequently observed in alectinib-resistant specimens than in crizotinib- or ceritinib-resistant specimens [56]; hence, alectinib followed by lorlatinib may be the best ALK-TKI sequence in such cases. Where resistant mutations other than G1202R are present, such as I1171T/N/S, V1180L, or L1196M, ceritinib may also be useful as a second-line treatment [56]. On the other hand, for patients who acquired resistance via bypass pathway activation, crizotinib (for MET gene amplification), ceritinib (for insulin-like growth factor [IGF]-1R activation), and alectinib or lorlatinib (for P-glycoprotein overexpression) [61] are the candidates of choice for second-line treatment.

The identification of the best treatment sequence or combination therapies for drug-resistant lung cancer has been a challenge [58]. Currently, several combination therapies with ALK-inhibitors and other molecular-targeting agents developed for lung cancers are ongoing in clinical trials. These include the following: 1) MEK-inhibitors: NCT03202940, alectinib combined with cobimetinib; NCT03087448, ceritinib combined with trametinib; 2) anti-vascular endothelial growth factor (VEGF) antibodies: NCT02521051, alectinib combined with bevacizumab; and 3) immunotherapy: NCT02393625, ceritinib combined with nivolumab; NCT01998126, crizotinib combined with nivolumab or ipilimumab; NCT02013219, alectinib combined with atezolizumab. Regarding combination therapy with ALK-TKIs and immune checkpoint inhibitors, Group E in the CheckMate 370 study was the phase 1/2 cohort testing the safety and tolerability of crizotinib plus nivolumab as a first-line treatment for ALK-positive NSCLC. However, 5/13 patients (38%) developed severe hepatic toxicities, and two died, leading to discontinuation of the treatment [62].

Recently, genome analyzing technology such as liquid biopsy has been evolving rapidly; hence, cancer gene profiles could soon be evaluable using blood droplet samples. If liquid biopsy becomes widespread, treatment strategies will improve because it will be possible to evaluate and select treatment options in a more timely manner [63].

On the other hand, delivering systemic chemotherapy is also essential to treat *ALK*-positive NSCLC patients. Pemetrexed is reported to be effective for *ALK*-positive NSCLCs [64,65]. Park *et al.* retrospectively reported that pemetrexed monotherapy as a second-line treatment showed a better overall response rate and mPFS in ALK-positive patients than in wild-type patients (29.0% vs. 11.8%; $p = 0.013$; 8.7 months vs. 1.9 months; $p < 0.001$). Hence, pemetrexed-containing chemotherapy is the treatment option of choice when the tumor is resistant to ALK-TKIs.

Conclusions

We reviewed the pivotal clinical studies and mechanisms of resistance to ALK-TKIs. *ALK*-positive NSCLCs acquire resistance via various mechanisms, making it a heterogeneous disease. Therefore, it is essential to develop next-generation treatment strategies, such as using next-generation ALK-TKIs for sec-

ondary mutations or combination therapy with ALK-TKIs and other TKIs.

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