Safety and efficacy of anaplastic lymphoma kinase tyrosine kinase inhibitors in non-small cell lung cancer (Review)

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Received February 26, 2020; Accepted July 31, 2020

DOI: 10.3892/or.2020.7851

Abstract. Since the discovery of targeted therapy with epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) have been introduced as the first-line treatment for non-small cell lung cancer (NSCLC) patients who carry sensitizing ALK-activating mutations. Compared with conventional chemotherapeutic regimens, small-molecule ALK-TKIs exhibit excellent clinical efficacy in ALK-positive NSCLC. A series of studies have indicated that ALK-TKI agents as the first-line treatment, including crizotinib, ceritinib, brigatinib, alectinib and entrectinib, can benefit patients with ALK-positive NSCLC. However, resistance to ALK-TKIs has emerged. ALK-TKIs are associated with significantly disabling and undesirable effects that adversely impact quality of life and compliance. This study reviews the pharmacodynamics, efficacy and safety of ALK-TKI agents in order to summarize these effects as well as the relevant management strategies. It is worth emphasizing that the frequency and severity of an adverse effect often varies across different trials.

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Key words: anaplastic lymphoma kinase tyrosine kinase inhibitors, crizotinib, ceritinib, brigatinib, alectinib, lorlatinib, entrectinib, safety, non-small cell, efficacy

1. Introduction

NSCLC is considered as one of the main causes of cancer-related deaths worldwide, accounting for approximately 80-85% of all histological subtypes of lung cancer (1,2). Patients with NSCLC are often diagnosed at advanced stages of the disease (3,4). The administration of conventional chemotherapeutic regimens only marginally improves the outcomes of these individuals. The median survival time of these individuals is less than one year after diagnosis and is driven by the molecular expression and genetic mutations of the tumor (3,4). The identification of patients harboring activated EGFR mutations and ALK rearrangements, which account for approximately 15 and 5% of advanced non-squamous lung carcinomas in Western countries (5), respectively, has led to the targeting of genomic alterations for the treatment of these patients. The development of EGFR-TKIs has fueled efforts to identify additional targeted therapies for NSCLC (6).

ALK, a transmembrane tyrosine kinase, belongs to the superfamily of insulin receptors that regulate cellular growth and may trigger neoplastic transformation, including platelet-derived growth factor receptors, the epidermal growth factor receptor, human epidermal growth factor receptor type 2, and insulin-like growth factor-1 receptors. ALK catalyzes the phosphorylation reaction of a tyrosine residue on a substrate protein (7,8). In fact, the activation mechanism of ALK is still not completely understood. Phosphorylation of these ALK residues can transmit ALK-mediated signals to downstream signaling pathways (7).

With the development of targeted therapy, the discovery that ALK mutations and rearrangements in NSCLC patients lead to abnormal signaling pathways has markedly changed the targeted therapy in this subset of patients (6). Aberrantly formed ALK oncogenes, mainly caused by fusion mutations, ALK gain-of-function mutations, or ALK amplification, have been identified in various cancers, such as NSCLC, anaplastic large-cell lymphoma (ALCL), inflammatory myofibroblastic tumors (IMTs), and neuroblastoma (9). In patients with NSCLC, the gene rearrangement of echinoderm microtubule-associated protein-like 4 (EML4) ALK is the most common ALK alteration, accounting for 4 to 7% of lung adenocarcinomas (9,10). Compared with conventional chemotherapeutic regimens, small-molecule ALK-TKIs exhibit excellent clinical efficacy

in ALK-positive NSCLC (11). In recent years, several ALK inhibitors have been developed to target dysregulated kinases. Crizotinib, which was launched in 2011, is a first-generation ALK inhibitor (12,13). The second-generation inhibitors include ceritinib, alectinib, brigatinib and entrectinib (Fig. 1). Lorlatinib (Table I) is a third-generation inhibitor (13-16). In addition, ensartinib, repotrectinib, and belizatinib are being investigated in ongoing clinical studies (17). It has been revealed that the median progression-free survival in patients using crizotinib was longer than that in patients undergoing chemotherapy in advanced ALK-positive lung cancer patients (12). However, resistance to the first-generation agent crizotinib has emerged in some clinical trials (18,19). Due to the poor blood-brain barrier penetration of crizotinib, brain metastases can present during the first year or two years of treatment (20).

This resistance of ALK is underpinned by different genetic mechanisms that include i) the development of secondary resistance mutations in ALK, such as L1196M (21,22), which most likely corresponds to a gatekeeper residue or a residue located in the ATP-binding pocket of a protein kinase that, when mutated, causes a change in the structure of the kinase that prevents TKI binding; ii) ALK copy number alterations; iii) aberrant activation of alternate kinases leading to ALK-independent growth, such as EGFR; and iv) epithelial-mesenchymal transition (23). L1196M (7%), G1269A (4%), C1156Y (2%), G1202R (2%), I1171T (2%), S1206Y (2%), and E1210K (2%) are the most common ALK-resistant mutations associated with crizotinib (21,22). The next-generation ALK inhibitors are generally active in crizotinib-resistant mutations, and novel mutations resistant to each of these agents have rapidly become apparent (22). Brigatinib was also found to inhibit nine different mutants with 3-54-fold greater potency than ceritinib and/or alectinib (24).

This review summarizes the pharmacology and clinical safety/efficacy associated with ALK-TKIs. The review is based principally on drug evaluation reports and the latest prescribing information provided by the United States Food and Drug Administration (FDA) supplemented as appropriate by published literature on agents under investigation. It is worth emphasizing that the frequency and severity of an adverse effect often varies across different trials, especially when there are different patient populations or indications under investigation, different treatment regimens and different sample sizes.

2. Approved ALK-TKIs

Thus far, six ALK-TKIs have been approved by the FDA and the European Medicines Agency (EMA). They are listed in Table I. The currently approved agents are different in terms of their selectivity and reversibility due to the presence of compound structures, which have been listed in Fig. 1. Table II revealed that the physicochemical properties of agents may be associated with compound structures.

First-generation ALK-TKI, crizotinib. Crizotinib is considered as a first-generation inhibitor of ALK indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive or c-ros oncogene 1 (ROS1)-positive (25). Crizotinib was approved by the US FDA in 2011. The recommended dosage of crizotinib is 250 mg orally twice daily with or without food (26). A pharmacokinetics study demonstrated that there was no statistically significant difference between fasted and fed in patients with crizotinib, while the exposure of crizotinib with a high-fat meal was slightly reduced compared with the exposure without a meal (27). Additional PK analyses (Table III) revealed that the bioavailability was 43%. Furthermore, ethnicity and age have been found to influence crizotinib PK (28). A clinical trial demonstrated that the mean C_{max} and AUC in Asian patients were 1.50 and 1.57, respectively, compared with those in non-Asian patients (29). A phase I dose-escalation study in adolescents revealed that the recommended dose exceeded the dosage in adults. Hepatic impairment and renal impairment affect the exposure of crizotinib in plasma (30,31). Therefore, crizotinib should be administered to these types of patients with an appropriate dose adjustment.

The concentration of crizotinib in plasma may be affected by its interaction with other drugs. Because crizotinib is metabolized by hepatic cytochrome enzyme P450, particularly CYP3A4 (28), the drug may be affected by inhibitors and inducers of CYP3A4, which are listed in able Table IV. Ketoconazole can increase the AUC_{inf} of crizotinib by 3.2-fold, and rifampin can decrease crizotinib exposure (32). Patients should thus be made aware of this fact when concomitantly using crizotinib and inhibitors and inducers of CYP.

Crizotinib has demonstrated safety and antitumor activity in patients with ALK-positive advanced NSCLC in a series of clinical trials. The PROFILE series showed consistent safety and efficacy superior to chemotherapy (33). The phase III (PROFILE 1007, PROFILE 1014), randomized, open-label study (34,35) was a milestone for ALK-TKIs, revealing superior progression-free survival (PFS) and objective response rates (ORRs) comparing crizotinib with standard chemotherapy. In the PROFILE 1007 study, which is the second-line setting, the median progression-free survival (PFS) of crizotinib compared with chemotherapy was 7.7 months vs. 3.0 months [hazard ratio (HR) 0.49; 95% confidence intervals (CIs), 0.37 to 0.64], and the response rate was higher with crizotinib than with chemotherapy [65% (95% CI, 58 to 72) vs. 20% (95% CI, 14 to 26)]. However, there was a statistically significant difference in the median overall survival between the two arms, which is listed in Table V. In the firstline setting (PROFILE 1014), the median PFS of crizotinib vs. chemotherapy was 10.9 vs. 7.0 (HR, 0.45; 95% CIs, 0.35 to 0.60). The objective response rates (ORR) was 74% vs. 45%. In another study (data from PROFILE 1007 and PROFILE 1014) (36), a randomized trial in Asian patients demonstrated the same result, revealing that the PFS was longer in the crizotinib group than in the chemotherapy group, with a median PFS of 8.1 and 2.8 months, respectively. However, due to ALK mutations and poor blood-brain barrier penetration, patients still experienced relapse and brain metastases within 11 months of treatment (37,38).

Second-generation ALK-TKIs

Ceritinib. Ceritinib is a tyrosine kinase inhibitor against multiple targets, including ALK, the insulin-like growth factor 1 receptor (IGF-1R), the insulin receptor (InsR), and ROS1 (39). As a selective oral ALK inhibitor, ceritinib has a 20 times

Table I. Currently approved ALK-TKIs.

Drug	FDA approval	EMA approval	Generation	Line of treatment	Targets	Broad indications	Company agreements
Crizotinib	2011	2012	First	First-line	ALK, ROS1, and MET	Metastatic NSCLC	Pfizer
Ceritinib	2014	2015	Second	First-line	ALK, IGF-1R, InsR, and ROS1	Metastatic NSCLC with ALK-positive tumours	Novartis
Brigatinib	2017	2018	Second	First-line	ALK, ROS1, IGF-1R, and FLT-3 as well as EGFR deletion and point mutations.	ALK-positive metastatic NSCLC	Ariad
Alectinib	2015	2016	Second	First-line	ALK and RET with CNS activity.	ALK-positive metastatic NSCLC	Hoffmann-La Roche
Lorlatinib	2018	2019	Third	-	ALK and ROS1 as well as TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK	ALK-positive metastatic NSCLC	Pfizer INC
Entrectinib	2019	2019	Second	First-line	(Trk) A/B/C, ROS1, NTRK, and ALK	Metastatic NSCLC with ROS1-positive tumours	Genentech

ALK-TKIs, anaplastic lymphoma kinase tyrosine kinase inhibitors; NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; ROS1, c-ros oncogene 1; MET, mesenchymal-epithelial transition factor; IGF-1R, the insulin-like growth factor-1 receptor; RET, rearranged during transfection; CNS, central nervous system; Trk A/B/C, tropomyosin receptor kinases A/B/C; NTRK, neurotrophic tyrosine receptor kinase.

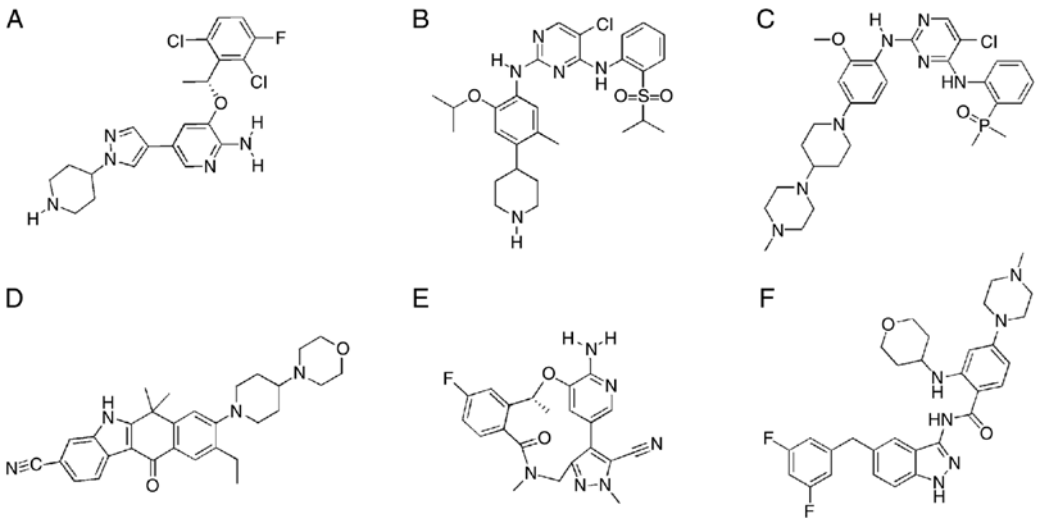

Figure 1. Structural formula of approved ALK-TKIs. (A) Crizotinib, (B) ceritinib, (C) brigatinib, (D) alectinib, (E) lorlatinib and (F) entrectinib. ALK-TKIs, anaplastic lymphoma kinase tyrosine kinase inhibitors.

greater potency than crizotinib against ALK-rearranged lung cancer cell lines in enzymatic assays (40). In addition, it can cross the blood-brain barrier (41). Ceritinib received approval from the FDA as a first-line treatment in patients with NSCLC, and in 2017, it was indicated for metastatic ALK-positive NSCLC. Ceritinib should be taken at a dosage of 450 mg once daily with food (42). The PK profile of ceritinib is listed in Table III and reveals that the drug is similar to crizotinib. Furthermore, ceritinib is mainly metabolized by P450 in the liver (37). Consequently, CYP3A inhibitors may increase the exposure of ceritinib in plasma. Warfarin, midazolam, and rifampin, which are strong CYP3A inhibitors, augment ceritinib in plasma (32).

Due to the poor blood-brain barrier penetration of crizotinib, a large number of patients develop CNS metastases and experience relapse within one year (37). Ceritinib has good blood-brain barrier penetration and can overcome some resistance caused by crizotinib (13). Ceritinib is sensitive to L1196M, G1269A, C1156Y, I1171T, and S1206Y (22). The ASCEND series revealed consistent and durable antitumor activity and tolerable safety in the ASCEND-1 and ASCEND-2 studies (11,37). Ceritinib provided a first-line treatment due to potent activity in crizotinib-naïve patients and significant improvements in PFS (16.6 vs. 8.1 months) compared with the chemotherapy group in the ASCEND-4 study (43). In the ASCEND-5 study (44), 231 patients with ALK-positive NSCLC were randomized. The results revealed that the median PFS resulting from ceritinib was longer than that resulting from chemotherapy [5.4 months (95% CI, 4.1-6.9) in the ceritinib arm vs. 1.6 months (95% CI, 1.4-2.8) in the chemotherapy arm (HR, 0.0.49; 95% CI, 0.36-0.67; Table V)].

Alectinib. Alectinib is a selective tyrosine kinase inhibitor that targets ALK and receptor of tyrosine kinase (RET); it has CNS activity and has been approved for advanced ALK-positive NSCLC patients with/without previous treatment with crizotinib (20). Alectinib has a five-fold higher potency than crizotinib for inhibiting ALK and maintains activity against several of the secondary mutants associated with resistance to crizotinib (45). Due to its clinical efficacy, good blood-brain barrier penetration, and tolerance, alectinib was approved in 2015 by the FDA as a front-line therapy for parents with advanced ALK-positive NSCLC (18,20). The recommended dose is 600 mg orally twice daily, and it should also be taken with food. A clinical trial demonstrated that a high-fat meal could increase the concentration of alectinib in plasma (46). Due to the similar structure between alectinib and ceritinib, the PK profiles of both are similar. The metabolism of alectinib occurs mainly through CYP3A4 in the liver, indicating that CYP3A4 inhibitors and inducers affect the PK of alectinib administration. The plasma protein binding rate was 99%. However, for patients with mild or moderate renal or hepatic impairment, there is no need to adjust the dose (20).

Alectinib is another ALK-TKI that can overcome the poor CNS penetration of crizotinib and crizotinib resistance, and it is sensitive to C1156, G1269A, S1206Y, and L1152R (19). The ALUR trial (47) revealed that the systemic and CNS efficacy in the alectinib arm was significantly improved compared with that in the chemotherapy arm for crizotinib-pretreated ALK-positive NSCLC patients; the median investigator-assessed PFS was 9.6 months vs. 1.4 months. Furthermore, the PFS assessed by the Independent Review Committee was 7.1 months for alectinib and 1.6 months for chemotherapy (HR, 0.32; 95% CI, 0.17-0.59, P<0.001). In a subgroup of patients with measurable baseline central nervous system (CNS) disease, the CNS ORR was significantly higher with alectinib (54.2%) vs. chemotherapy (0%; P<0.001) (47). The J-ALEX and ALEX trials (48,49), which compared alectinib with crizotinib in treatment-naïve patients with advanced ALK-positive NSCLC, were phase III studies that revealed the superiority of alectinib over crizotinib. In the J-ALEX trials, the median PFS was not yet reached in the alectinib cohort [95% CI, 20.3 months-not estimable (NE)] and was 10.2 months in the crizotinib cohort (95% CI, 8.2-12) in the preplanned interim analysis. ALEX results were similar to those in J-ALEX, with significant improvements in median PFS [alectinib (95% CI, 17.7 months-NE) vs. crizotinib 11.1 months (95% CI, 9.1-13.1)].

Table II. Physicochemical properties of approved ALK-TKIs.

Properties	Crizotinib	Ceritinib	Brigatinib	Alectinib	Lorlatinib	Entrectinib
Molecular formula (mg/mole)	450.34	558.14	584.10	482.62	406.41	560.64
Molecular weight	$C_{21}H_{22}Cl_2FN_5O$	$C_{28}H_{36}ClN_5O_3S$	$C_{29}H_{39}ClN_7O_2P$	$C_{30}H_{34}N_4O_2$	$C_{21}H_{19}FN_6O_2$	$C_{31}H_{34}F_2N_6O_2$
Octanol/water	1.65 (pH 7.4)	5.23	5.17	NA	2.45 (pH 9)	NA
Water solubility	0.00611 mg/ml	0.00222 mg/ml	0.022 mg/ml	NA	32.38-0.17 (pH 2.55-8.02)	NA
pKa	9.4 and 5.6	9.7 and 4.1	NA	7.05 (base)	4.9	NA

ALK-TKIs, anaplastic lymphoma kinase tyrosine kinase inhibitors; NA, not available; pKa, symbol for acid dissociation constant at logarithmic scale.

Table III. Clinically relevant pharmacokinetics of currently approved ALK-TKIs.

PK parameter	Crizotinib	Ceritinib	Brigatinib	Alectinib	Lorlatinib	Entrectinib
Available dosage strengths[a] (mg)	250/200	150	30/90	150	25/100	100/200
Recommended dose	250 mg bid	450 qd	90 mg qd	600 mg bid	100 mg qd	600 mg qd
T_{max}	4-6 h	4-6 h	1-4 h	4 h	2 h	4-6 h
Bioavailability	43%	NA	NA	37%	NA	NA
Plasma protein binding	91%	97%	66%	99%	66%	>99%
$t_{1/2}$	42 h	41 h	25 h	33 h	24 h	20-40 h
Metabolism	CYP3A	CYP3A	CYP2C8, CYP3A4	CYP3A4	CYP3A4, UGT1A4	CYP 3A4

[a]Available dosage strengths signify the strength of a drug product, which indicates the amount of active ingredient in each dosage. ALK-TKIs, anaplastic lymphoma kinase tyrosine kinase inhibitors; CYP, cytochrome P450; UGT, UDP-glucuronosyltransferase; NA, not available, bid, *bis in die*; qd, *quaque die*.

Table IV. DDI between ALK-TKIs and inhibitors/inducers of CYP.

Drug	DDI	Mechanism	Consequences	Current recommendations
Crizotinib	Ketoconazole	CYP3A4 inhibitor	AUC_{inf} augmentation of crizotinib with ketoconazole 3.2-fold	CYP3A4 inhibitors or inducers significantly affect the pharmacokinetics of crizotinib after single- and multiple-dose administration
	Rifampin	CYP3A4 inducer	AUC_{inf} diminution of crizotinib with rifampin 82%	
	Midazolam	CYP3A4 inhibitor	It can increase midazolam plasma AUC by 3.7-fold	
Ceritinib	PPI	P-gp inhibitor	Augmentation of ceritinib with ketoconazole C_{max} by 22% and AUC by 186%	The drug label of ceritinib warns against the co-administration of strong CYP3A inhibitors. It is preferable to avoid the co-administration of strong CYP3A inducers
	Warfarin	Strong CYP3A inhibitor		
	Midazolam	Strong CYP3A inhibitor		
Brigatinib	Rifampin	Strong CYP3A inducer	The co-administration of rifampin decreases the AUC_{inf} of ceritinib by 70%	
	Itraconazole	CYP3A inducer	Augmentation of ceritinib with itraconazole C_{max} by 21% and AUC by 101%	
	Ketoconazole	Strong CYP3A inhibitor		
	Gemfibrozil	Strong CYP2C8 inhibitor	Diminution of brigatinib with gemfibrozil AUC and C_{max} by 12% and 41%, respectively.	The effects of gemfibrozil on the pharmacokinetics of brigatinib are not clinically significant; however, the concomi tant use of brigatinib with strong CYP3A inhibitors needs to be avoided
	Rifampin	CYP 3A4 inducer	Rifampin decreases brigatinib C_{max} and AUC_{inf} by 60% and 80%, respectively	The co-administration of strong CYP3A inducers with brigatinib needs to be avoided
Alectinib	Posaconazole	CYP 3A4 inhibitor		
	Esomeprazole	CYP 3A4 inhibitor		
	Rifampin	CYP 3A4 inhibitor	Diminution of alectinib and M4 with rifampin AUC and C_{max} by 26.8% and 48.6% and 220% and 179%, respectively	
	Midazolam	CYP 3A4 substrate	Alectinib does not affect midazolam exposure	
Lorlatinib	Rifampin	CYP 3A4 inducer	UK	UK

ALK-TKIs, anaplastic lymphoma kinase tyrosine kinase inhibitors; AUC, area under the curve; AUC_{inf}, AUC from zero to infinity; C_{max}, maximum plasma concentration; CYP, Cytochrome P450; CYP 3A4, Cytochrome P450 3A4; DDI, drug-drug interaction; P-gp, P-glycoprotein; PPI, Proton-pump inhibitor; UK, unknown.

Table V. Pivotal clinical efficacy of ALK-TKIs for the treatment of NSCLC.

Study (n), (Ref.)	TKI treatment	Control	Targeted patients	Median PFS (months) [HR; 95% CIs][a]	ORR%[a]	Median OS (HR; 95% CIs][a]
PROFILE 1007 (n=347), (34)	Crizotinib	Docetaxel or Pemetrexed	Locally advanced or metastatic ALK-positive lung cancer with one prior platinum-based regimen	7.7 vs. 3.0 [0.49; 0.37 to 0.64]	65% vs. 20%	20.3 vs. 22.8 [1.02; 0.68 to 1.54]
PROFILE 1014 (n=343), (35)	Crizotinib	Pemetrexed plus a platinum or carboplatin	Advanced ALK-positive non-squamous NSCLC patients without previous systemic treatment	10.9 vs. 7.0 [0.45; 0.35 to 0.60]	74% vs. 45%	NR vs. 47.5 [0.76; 0.548 to1.053]
PROFILE 1029 (n=207), (61)	Crizotinib	Docetaxel or Pemetrexed	Previously untreated ALK-positive advanced NSCLC	11 vs. 6.8 [0.402; 0.286 to 0.565]	87.5% vs. 45.6%	NA
ASCEND-4 (n=376), (43)	Ceritinib	Platinum-based chemotherapy	ALK-rearranged non-squamous NSCLC	16.6 vs. 8.1 [0.55; 0.42 to 0.73]	NA	NR vs. 26.2 [0.73; 0.50 to 1.08]
ASCEND-5 (n=231), (44)	Ceritinib	Docetaxel or Pemetrexed	ALK-rearranged NSCLC patients with previous chemotherapy and crizotinib	5.4 vs. 1.6 [0.49; 0.36 to 0.67]	39.1% vs. 6.9%	NA
ALUR (n=107), (47)	Alectinib	Docetaxel or Pemetrexed	Advanced/metastatic ALK-positive NSCLC	7.1 vs. 1.6 [0.32; 0.17 to 0.59]	36.1% vs. 11.4%	12.6 vs. NR [0.89; 0.35 to 2.24]
J-ALEX (n=207), (48)	Alectinib	Crizotinib	ALK-positive non-small cell lung cancer, who were chemotherapy-naive or had received one previous chemotherapy regimen	NR vs. 10.2 [0.34; 0.17 to 0.71]	-	NR
ALEX (n=303), (49)	Alectinib	Crizotinib	Previously untreated, advanced ALK-positive NSCLC	NR vs. 11.1 [0.47; 0.34 to 0.65]	NA	NA [0.76; 0.48 to 1.20]
ALTA-1L (n=275), (53)	Brigatinib	Crizotinib	Advanced ALK-positive NSCLC	NR vs. 9.8 [0.49; 0.33 to 0.74]	71% vs. 60%	NA

ALK-TKIs, anaplastic lymphoma kinase tyrosine kinase inhibitors; PFS, progression-free survival; HR, hazard ratio; Cis, confidence intervals; NSCLC, non-small cell lung cancer; NA, not available; ORR, overall response rate; OS, overall survival; NR, not reached; NA, not available.

Table VI. AEs with ALK-TKIs across pivotal phase III clinical trials on advanced NSCLC.

Study (n)[a], (Ref.)	Time[b]	Common AEs (number and percentage of all grades)	Common grade ≥3AEs (number and percentage)	Dose change related to AEs
PROFILE 1007 (n=173), (34)	February 2012	Vision disorder (103; 60%) Diarrhea (103; 60%) Nausea (94; 55%) Vomiting (80; 47%)	Elevated aminotransferase levels (27; 16%) Dyspnea (7; 13%) Constipation (4; 2%) Fatigue (4; 2%)	-
PROFILE 1014 (n=171), (35)	January 20, 2011	Vision disorder (122; 71%) Diarrhea (105; 61%) Vomiting (78; 46%) Constipation (74; 43%)	Elevated aminotransferases (24; 14%) Neutropenia (19; 11%) Dyspnea (5; 3%) Fatigue (5; 3%)	-
PROFILE 1029 (n=104), (61)	September 2012	Increased transaminase level (72; 69.2%) Diarrhea (61; 58.7%) Vision disorder (58; 55.8%) Vomiting (55; 52.9%)	Neutropenia (17; 16.3%) Increased transaminase level (12; 11.5%) Leukopenia (3; 2.9%) Anemia (3; 2.9%)	-
ASCEND-4 (n=189), (43)	Aug 19, 2013	Diarrhea (160; 85%) Nausea (130; 69%) Vomiting (125; 66%) Alanine aminotransferase increased (114; 60%)	Alanine aminotransferase increased (58; 31%) Gamma-glutamyltransferase increased (54; 29%) Aspartate aminotransferase increased (32; 17%) Blood alkaline phosphatase increased (14; 7%)	Dose adjustment or interruption were reported in 152 (80%)
ASCEND-5 (n=115), (44)	June 28, 2013	Diarrhea (78; 68%) Nausea (67; 58) Vomiting (51; 44%) ALT concentration increased (25; 22%)	ALT concentration increased (22; 19%) GGT concentration increased (21; 18%) AST concentration increased (15; 13%) Vomiting (9; 8%) Nausea (9; 8%)	Dose adjustment or interruption or delay were reported in 92 (80%)
ALUR (n=72), (47)	-	Fatigue (4; 4.7) Constipation (13; 18.6%) Neutropenia (2; 2.9%) Diarrhea (2; 2.9%) Dyspnea (6; 8.6%)	Asthenia (2; 2.9%) Pneumonia (2; 2.9%) Syncope (2; 2.9%) Acute kidney injury (2; 2.9%)	Dose adjustment or interruption in 20 (28.6%)
J-ALEX (n=103), (48)	Nov 18, 2013	Constipation (36; 35%) Nasopharyngitis (21; 20%) Blood creatine phosphokinase increased (18; 17%) Dysgeusia (19; 18%)	Blood creatine phosphokinase increase (5; 5%) Respiratory, thoracic, mediastinal disorders and interstitial lung disease (5; 5%) Maculopapular rash (3; 3%) Neutrophil count decrease (2; 2%) Electrocardiogram QT prolonged (2; 2%)	Dose adjustment or interruption in 39 (38%)

Table VI. Continued.

Study (n)[a], (Ref.)	Time[b]	Common AEs (number and percentage of all grades)	Common grade ≥3AEs (number and percentage)	Dose change related to AEs
ALEX (n=152), (49)	August 18, 2014	Anemia (30; 20%)	Blood bilirubin increased (3; 2%)	Dose adjustment or interruption 70 (46%)
		Peripheral edema (26; 17%)	Anemia (7; 5%)	
		Myalgia (24; 16%)	ALT increased (7; 5%)	
		Blood bilirubin increased (23; 15%)	AST increased (8; 5%)	
ALTA-1L (n=136), (53)	April 2016	Diarrhea (67; 49%)	Increased blood creatine kinase level (22; 16%)	Dose adjustment in 12%
		Increased blood creatine kinase level (53; 39%)	Increased lipase level (18; 13%)	
		Nausea (36; 26%)	Hypertension (13; 10%)	
		Cough (34; 25%)	Increased amylase level (7; 5%)	

[a]The number of patients in the treatment group. [b]Subject to time of first posted for clinical trial. Common AEs define the top four AEs, unless there are multiple rankings in the fourth. ALK-TKIs, anaplastic lymphoma kinase tyrosine kinase inhibitors; NSCLC, non-small-cell lung cancer; AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; QT, the time between the start of the Q-wave and the end of the T-wave; GGT, gamma-glutamyl transpeptidase.

Brigatinib. Brigatinib is a tyrosine kinase inhibitor with broad-spectrum activity against ALK, ROS1, the insulin-like growth factor-1 receptor (IGF-1R), and Fms-like tyrosine kinase 3 (FLT-3), as well as EGFR deletions and point mutations, including L1152R, V1180L, G1202R, R1275Q, T790M, C797S, and L858R (24,25,50). Brigatinib has a 12-fold higher potency than crizotinib for inhibiting ALK. It inhibits crizotinib-, ceritinib-, and alectinib-resistant ALK mutants (24). Brigatinib received approval from the US FDA in 2017 and is indicated for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Brigatinib should be taken at a dosage of 90 mg orally once daily for the first 7 days. If patients are tolerant, the dosage should be increased to 180 mg orally once daily. It may be taken with or without food (51). The PK profile of brigatinib is presented in Table III (52). Because brigatinib is primarily metabolized by CYP2C8 and CYP3A (52), this strong inhibitor and inducer, respectively, must affect its exposure. Ariad Pharmaceuticals is investigating the drug-drug interaction between brigatinib and midazolam (52).

Although ceritinib and alectinib can overcome resistance mutations associated with crizotinib, some new resistance mutations still arise. It has been reported that there are seventeen mutations associated with crizotinib, ceritinib and alectinib, including G1202R (22). Brigatinib exhibited activity against this and other mutations. ALTA-1L is a pivotal trial of brigatinib for 1st-line treatment (53). In a randomized, open-label study (53), 275 patients with advanced ALK-positive NSCLC who had been treated with ALK inhibitors were randomly assigned to receive brigatinib or crizotinib. At the follow-up of 12 months, the rate of PFS in the brigatinib arm was higher than that in the crizotinib arm [67% (95% CI, 56 to 75) vs. 43% (95% CI, 32 to 53)].

Entrectinib. Entrectinib is a selective inhibitor of the tyrosine kinases tropomyosin receptor kinases (Trk) A/B/C, ROS1 and ALK with central nervous system activity (54,55). Entrectinib is 30 times more potent against ROS1 than crizotinib (54). It was approved by the FDA in 2019 as a first-line treatment for adult patients with ROS1-positive metastatic NSCLC and for adult and pediatric patients (12 years of age and older) with solid tumors (55). Adult patients with ROS1-positive metastatic NSCLC and neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion-positive solid tumors should be administered a dosage of 600 mg orally once daily. For patients 12 years and older with *NTRK* gene fusion-positive solid tumors, the recommended dosage is based on body surface area (BSA) (55). The PK profile of entrectinib is listed in Table III (56). The clinical activity of entrectinib was assessed in four trials (SATARTRK-1/SATARTRK-2/SATARTRK-NG/ALKA-372-001) (57), and the efficacy of entrectinib was assessed in patients with ROS1-positive NSCLC [ORR 78%;65%, 89%], DOR≥9 months 70%). Responses were observed in SATARTRK-1 ALK-rearranged cancer patients (n=7) with an ORR of 57% and a median PFS of 8.3 months.

Third-generation ALK-TKIs

Lorlatinib. Lorlatinib is a kinase inhibitor with activity against ALK and ROS1 as well as TYK1, FER, FPS, TRKA/B/C, FAK, FAK2, and ACK, and it can penetrate the blood-brain

Table VII. On-going clinical trials of ALK-TKIs in NSCLC.

NCT	Drug	Identifier	Sponsor	No. of samples	Phase	Primary endpoint
NCT03874273	Crizotinib	Inflammatory myofibroblastic tumour	Federal Research Institute of Pediatric Hematology, Oncology and Immunology	25	II/III	ORR
NCT03620643	Crizotinib	Lobular breast carcinoma gastric cancer	Royal Marsden NHS Foundation Trust	58	II	Percentage of participants with objective responses
NCT03088930	Crizotinib	Lung cancer, NSCLC	University of Colorado, Denver	18	II	Objective tumour response rate
NCT03646994	Crizotinib	ROS1 arranged non-squamous NSCLC	Hunan Province Tumor Hospital	40	II	PFS
NCT03672643	Crizotinib	ALK or ROS1-positive NSCLC	Pfizer	75	IV	Long-term safety of crizotinib
NCT02419287	Crizotinib	Anaplastic large cell lymphoma, ALK-positive	University of Milano Bicocca	12	II	ORR Duration
NCT03647111	Crizotinib	ALK rearranged non-squamous NSCLC	Hunan Province Tumor Hospital	120	II	PFS
NCT03052608	Lorlatinib/ Crizotinib	ALK-positive NSCLC	Pfizer	280	III	PFS
NCT02201992	Crizotinib	Stage IB-IIIA NSCLC that has been removed by surgery and ALK fusion mutations	ECOG-ACRIN Cancer Research Group	168	III	OS
NCT02679170	Crizotinib	Advanced/Metastatic NSCLC	Pfizer	100	II	Incidence of ALK-positive NSCLC PFS
NCT03087448	Ceritinib + Trametinib	NSCLC	University of California, San Francisco	69	I/II	MTD
NCT02299505	Ceritinib	NSCLC	Novartis Pharmaceuticals	306	I	Plasma concentration of ceritinib
NCT01828099	Ceritinib/ Chemotherapy	NSCLC	Novartis Pharmaceuticals	375	III	PFS
NCT02513667	Ceritinib	ALK-positive NSCLC	University of Texas Southwestern Medical Center	33	II	PFS
NCT02393625	Ceritinib With Nivolumab	ALK-positive NSCLC	Novartis Pharmaceuticals	57	I	MTD, ORR
NCT01828112	Ceritinib/ Chemotherapy	NSCLC previously treated with chemotherapy (platinum doublet) and crizotinib	Novartis Pharmaceuticals	232	III	PFS
NCT03501368	Ceritinib	Melanoma Unresectable Melanoma Advanced Melanoma	H. Lee Moffitt Cancer Center and Research Institute	27	II	ORR
NCT03611738	Ceritinib + Docetaxel	ALK-negative, EGFR WT advanced NSCLC	H. Lee Moffitt Cancer Center and Research Institute	48	I	MTD Phase Ib: OR

Table VII. Contunded.

NCT	Drug	Identifier	Sponsor	No. of samples	Phase	Primary endpoint
NCT02321501	Ceritinib + Everolimus	ALK-positive locally advanced or metastatic solid tumors or stage IIIB-IV NSCLC	M.D. Anderson Cancer Center	66	I	MTD
NCT03399487	Ceritinib	NSCLC harbouring ROS1 rearrangement	Yonsei University	46	II	ORR
NCT01964157	Ceritinib	NSCLC, cancer harbouring ROS1 rearrangement	Yonsei University	32	II	ORR
NCT03445000	Alectinib	Advanced NSCLC	European Thoracic Oncology Platform	44	II	Best overall response
NCT02521051	Alectinib + Bevacizumab	NSCLC	Massachusetts General Hospital	43	I/II	RP2D
NCT03202940	Alectinib + Cobimetinib	Advanced ALK-rearranged (ALK+) NSCLC	Massachusetts General Hospital	31	IB/II	MTD
NCT03271554	Alectinib	ALK-positive, locally advanced or metastatic NSCLC	Hoffmann-La Roche	167	II	Percentage of participants with AEs
NCT03596866	Brigatinib/ Alectinib	ALK+NSCLC who have progressed on crizotinib	Ariad Pharmaceuticals	246	III	PFS
NCT03194893	Alectinib/ Crizotinib	ALK+NSCLC rearranged during transfection (RET)-positive cancer	Hoffmann-La Roche	200	III	Number of patients with SAEs, non-SAEs and AEs of special interest
NCT03420742	Brigatinib	ALK-positive or ROS1-positive solid tumors	Ariad Pharmaceuticals	20	I	AUC, C_{max}, T_{max}
NCT03410108	Brigatinib	ALK-positive NSCLC	Takeda	110	II	ORR 12 months PFS Rate
NCT03535740	Brigatinib	ALK^+, advanced NSCLC progressed on alectinib or ceritinib (ALTA-2)	Ariad Pharmaceuticals	103	II	ORR
NCT03596866	Brigatinib/ Alectinib	Advanced ALK+NSCLC participants who have progressed on crizotinib (ALTA-3)	Ariad Pharmaceuticals	246	III	PFS
NCT02706626	Brigatinib	NSCLC	Criterium, Inc.	120	II	ORR
NCT02094573	Brigatinib	ALK-positive, NSCLC previously, treated with Crizotinib	Ariad Pharmaceuticals	222	II	ORR
NCT01449461	Brigatinib	Antitumour activity of the oral ALK/EGFR	Ariad Pharmaceuticals	137	I/II	RP2D ORR
NCT03707938	Brigatinib	Patients with Stage IV or recurrent NSCLC	M.D. Anderson Cancer Center	35	I	Incidence of AE
NCT03389399	Brigatinib	NSCLC	Academic Thoracic Oncology Medical Investigators Consortium	43	I	The incidence of EOPEs (time frame: 8 days)
NCT03546894	Any FDA Approved ALK Inhibitors	Anaplastic lymphoma kinase-positive Carcinoma NSCLC	Millennium Pharmaceuticals, Inc.	160	II	Prescriber-confirmed PFS

Table VII. Contunded.

NCT	Drug	Identifier	Sponsor	No. of samples	Phase	Primary endpoint
NCT03909971	Lorlatinib	ALK inhibitor-treated ALK-positive NSCLC	Pfizer	100	II	OR
NCT03505554	Lorlatinib	Relapsed ALK-positive lymphoma	University of Milano Bicocca	12	II	ORR
NCT04127110	Lorlatinib	ALK-positive NSCLC patients	European Organisation for Research and Treatment of Cancer-EORTC	84	II	PFS
NCT03726333	Lorlatinib	Advanced cancers	Pfizer	76	I	Plasma lorlatinib AUC_{24} at steady state
NCT03961997	Lorlatinib	Healthy participants	Pfizer	16	I	AEs
NCT03439215	Lorlatinib	Crizotinib pretreated ROS1-positive NSCLC	Fondazione Ricerca Traslazionale	20	II	Response rate to PF-06463922 in patients with ROS1 translocation resistant to crizotinib
NCT02927340	Lorlatinib	Advanced ALK and ROS1 rearranged lung cancer with CNS metastasis	Massachusetts General Hospital	30	II	Intracranial disease control rate
NCT03107988	Lorlatinib	Neuroblastoma	New Approaches to Neuroblastoma Therapy Consortium	40	I	RP2D, AE
NCT03542305	Lorlatinib	Renal impairment	Pfizer	32	I	AUC, C_{max}
NCT03727477	Lorlatinib	NSCLC	Intergroupe Francophone de Cancerologie Thoracique	250	II	PFS
NCT03796260	Entrectinib	Healthy participants	Genentech, Inc.	14	I	AUC, C_{max}
NCT02568267	Entrectinib	Solid tumours harbouring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK gene rearrangements (fusions) (STARTRK-2)	Hoffmann-La Roche	300	II	ORR
NCT02650401	Entrectinib	Children and adolescents with solid tumours CNS tumours	Hoffmann-La Roche	65	I	MTD, RP2D, ORR
NCT02767804	Ensartinib	NSCLC	Xcovery Holding Company, LLC	290	III	PFS
NCT04056572	TQ-B3139	ALK-positive NSCLC previously treated with Crizotinib	Chia Tai Tianqing Pharmaceutical Group Co., Ltd.	135	II	ORR
NCT04009317	TQ-B3139	ALK-positive NSCLC	Chia Tai Tianqing Pharmaceutical Group Co., Ltd.	260	III	PFS

ORR, overall response rate; NSCLC, non-small-cell lung cancer; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ROS1, c-ros oncogene 1; NTRK, neurotrophic tyrosine kinase; CNS, central nervous system; PFS, progression-free survival; OS, overall survival; MTD, maximum tolerated dose; OR, overall response; RP2D, recommended phase II dose; AEs, adverse events; SAEs, serious adverse events; non-SAEs, non-serious adverse events; EOPEs, early onset pulmonary events; AUC, area under the curve; C_{max}, maximum plasma concentration; Tmax, time to achieve peak concentration.

barrier to overcome known ALK resistance mutations (58). In addition, lorlatinib is effective against all known resistant mutants of first- and second-generation ALK inhibitors, such as crizotinib-resistant ALK G1202R and ROS1 G2032R mutants (16). Lorlatinib demonstrates significantly improved (>50-fold) inhibitory potency (59). Lorlatinib received approval from the FDA in 2018 and is indicated for the treatment of patients with ALK-positive metastatic NSCLC whose disease has progressed while taking crizotinib/ceritinib/alectinib as first-line ALK inhibitors for metastatic disease and at least one other ALK inhibitor for metastatic disease. The recommended dosage of lorlatinib is 100 mg orally once daily (58). The PK profile is demonstrated in Table III. Because lorlatinib has high membrane and blood-brain barrier permeability, it is transported by ABCB1 and ABCG2 since inhibitors of the transporters ABCB1 and ABCG2 influence the concentration of lorlatinib in the brain (60).

Lorlatinib is active against all known acquired resistance mutations associated with earlier TKIs. A phase I dose-escalation study of lorlatinib (NCT03052608) in an array of cancer indications, including ALK-positive NSCLC with two or more previous ALK TKI treatments and ALK-positive NSCLC with brain metastases, demonstrated that lorlatinib was effective for NSCLC patients with acquired resistance to ALK TKIs (33). These impressive results were confirmed by a phase II trial with expansion cohorts in patients with ALK-positive or ROS1-positive advanced NSCLC, revealing that the objective response was 47% in patients with at least one prior ALK TKI treatment and that the ORR was 90% in ALK-positive and treatment-naïve patients (33).

3. Safety evaluation

Data from certain clinical trials have reported that nausea/vomiting and diarrhea are the most common side effe cts (34,35,43,44,47-49,53,61), which are listed in Table VI. Pneumonitis/interstitial lung disease/pulmonary disease has been described as a relatively rare but serious side effect (62). In ASCEND-1, which aimed to evaluate the safety of ceritinib in a multicenter, single-arm, open-label clinical study of 255 ALK-positive patients, up to 5% of patients experienced adverse reactions, including (but not limited to) pneumonia, respiratory failure, ILD/pneumonitis, pneumothorax, and gastric hemorrhage. Even fatal events were reported (occurring in 0.2% of patients) (26).

Hepatotoxicity. Hepatotoxicity is reported relatively frequently in preapproved clinical trials for TKIs as a serious class-related safety issue (63). Concurrently, hepatotoxicity is the leading cause of drug withdrawal in the market. ALK inhibitors are also associated with hepatotoxicity (63). A systematic meta-analysis of clinical trials assessed the incidence and risk of ALK inhibitors (64). Among 1,908 patients from 10 clinical trials, aspartate aminotransferase (AST) elevation accounted for 25.2%, and alanine transaminase (ALT) elevation accounted for 26.0%.

In a clinical trial, hepatobiliary disorders also appeared in patients treated with alectinib, and these disorders included increased levels of AST (3.7%), ALT (3.7%) (65) and bilirubin (3.2%) (64); 1.2-1.5% of the patients withdrew from treatment due to these adverse reactions (ARs). In the NP28761 study, the levels of alanine aminotransferase and aspartate aminotransferase in patients with alectinib increased by 6 and 5%, respectively, and two patients withdrew from the study due to hepatotoxicity. In another trial, blood bilirubin levels increased by 15% (19).

A meta-analysis revealed that the frequencies of grade ≥3 hepatotoxicity induced by ceritinib are greater than those induced by crizotinib or alectinib (66). IGF receptors play an important role, as revealed by the fact that ceritinib inhibits insulin-like growth factor 1 (IGF-1) and insulin receptors and that the IGF receptor is ubiquitous at the cell surface and exists on the surface of cells. Therefore, patients who use alectinib and brigatinib have lower hepatotoxicity than patients who use ceritinib and crizotinib (66). Two analyses reported that the hepatotoxicity induced by alectinib was lower than that induced by crizotinib and ceritinib (64,67).

Although a dose reduction or interruption can occur due to the hepatotoxicity associated with ALK inhibitors, there have been limited studies on the influencing factors. Jung *et al* (68) reported that the presence of liver disease or HBV and the use of an H2 antagonist or H2 antagonist/proton pump inhibitor were the main risk factors for hepatotoxicity induced by crizotinib. A study (67) reporting a histological analysis of patients with acute hepatitis who were treated with alectinib demonstrated that acute hepatitis led to significantly high levels of hepatotoxicity.

Gastrointestinal toxicities. The common toxicities associated with ALK-TKIs are gastrointestinal toxicities, including nausea, vomiting, diarrhea and constipation (65). Although the severity of these toxicities is mild, they are potentially life threatening and can be distressing for patients, affecting their quality of life. Severe diarrhea can result in electrolyte imbalance, renal insufficiency, malnutrition, and extreme dehydration, all of which can lead to cardiovascular compromise and death (69). In a phase I study, a large number of patients (96%; 14% severe cases) experienced gastrointestinal (GI) adverse events (AEs) as a result of taking the recommended dose of ceritinib (70). In the XALKORI (n=171) study, up to 61% of patients who took crizotinib experienced diarrhea, with grade 3-4 diarrhea accounting for 2% across all clinical trials (26).

GI AEs are one of the most common reasons for dose modification (38% of patients) (70). Other severe gastrointestinal toxicities, such as vomiting and nausea, occur in patients treated with brigatinib (24%, grade 3-4 1.8%; 33%, grade 3-4 0.9%) (71). The incidence and severity of gastrointestinal adverse reactions, including diarrhea, nausea, and vomiting, account for 56/45/35% of patients, respectively, and can be reduced with a dose of 450 mg ceritinib taken with food. Nausea (1.8%) is one of the most frequent adverse reactions that leads to dose reduction in patients taking crizotinib (65). Schaefer and and Baik (70) suggested strategies for potential GI AEs resulting from ceritinib treatment in nine patients, and these recommendations can prevent the need for dose reduction due to GI AEs so that patients can continue taking the prescribed dose (750 mg/d ceritinib dose). Regimens A and B can be implemented as follows: Regimen A consists of ondansetron and diphenoxylate/atropine or loperamide taken 30 min prior to the dose of ceritinib, and Regimen B consists of dicyclomine, which should be taken with the first dose of ceritinib; ondansetron, which should be taken 30 min prior to

the dose of ceritinib for the first seven doses; and loperamide, which should be taken as needed with the onset of diarrhea. Although these strategies are not currently recommended or implemented in clinical studies, they provide an option for physicians.

Interstitial lung disease (ILD). ILD has been described as a relatively rare but fatal complication associated with tyrosine kinase inhibitors (72). Lung toxicity has been reported in patients taking ALK-TKIs such as crizotinib, ceritinib, and alectinib, with incidence rates of 1.8, 1.1, and 2.6%, respectively (72). In a retrospective study, only 1.2% of 1,669 patients treated with crizotinib in clinical trials exhibited crizotinib-related ILD. However, 50% of those patients succumbed due to ILD (73). Treatment-related deaths (TRDs) were reported in 12 of the 1,365 evaluable patients, resulting in an overall prevalence of 0.9%. The main cause of death was ILD or pneumonitis (66). Severe pulmonary adverse reactions consistent with ILD or pneumonitis occurred with 90 mg brigatinib treatment in 3.7% of the overall patients and 9.1% of patients in the 90/180 mg group (74).

The risk factors for ILD are not fully understood, but some studies have reported that smoking history, previous or concomitant ILD, and comorbid pleural effusion are associated with ILD, regardless of patient characteristics (73). In other words, ILD represents a potential reason for pulmonary harm. The management strategies for this toxicity are mainly discontinuation and steroid treatment. However, rechallenge with another ALK inhibitor in patients with a previous history of ALK-related ILD and ILD risk factors must be approved via a collegial decision. For example, brigatinib was used in a patient with ALK-rearranged lung adenocarcinoma who developed crizotinib-induced ILD. A cross-link with lung toxicity was not demonstrated in this patient; rather, the patient benefited from that treatment (75).

Cardiac AEs. Cardiac AEs such as Corrected QT (the time between the start of the Q-wave and the end of the T-wave) Interval (QTc) interval prolongation/bradycardia have been reported in patients taking ceritinib/crizotinib/alectinib and brigatinib (26,71,76,77). Symptomatic bradycardia has reportedly emerged in patients treated with alectinib in the NP28761, NP28673 and ALEX studies (78), accounting for 8%. The heart rates of these patients were less than 50 beats per minute (bpm). Furthermore, patients taking ceritinib experienced QTc interval prolongation and bradycardia. Heart rate decreases and sinus bradycardia were observed in some patients treated with crizotinib, with a reduction of 2.5 bpm.

The most effective way to prevent cardiac AEs is to monitor the heart rate and blood pressure of patients regularly during treatment with ALK-TKIs because bradycardia cannot be avoided. Products that cause bradycardia should be avoided when combined with ceritinib/crizotinib/alectinib and brigatinib.

4. Future directions

Since the discovery of targeted therapy with ALK, it has been reported that compared to chemotherapeutic agents, ALK inhibitors show improvements in PFS, ORR, and quality of life (2). Furthermore, several new compounds have been synthesized and are under investigation in different phases of clinical trials (Table VII). Based on our own experience, we encourage the early review of potential side effects to minimize any impact of AEs on the quality of life of patients and to help avoid any unnecessary dose reductions or early discontinuations of this effective treatment. With the development of resistance to ALK-TKIs, later-generation ALK-TKIs have been discovered to improve safety profiles (17). However, with disease progression in patients, the switching of ALK-TKIs can be used to identify the mutations and rearrangements of ALK (11,17). In other words, it is helpful to understand the resistance mechanisms. While the current technology used for liquid biopsy to detect late mutations in ALK is well justified, greater efforts are also required to minimize the clinical risks that adversely impact morbidity and quality of life. Finally, chemotherapy is also a valid choice for patients with ALK-positive metastatic NSCLC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

WL wrote the paper. WW reviewed and edited the manuscript. Both authors read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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