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REVIEW

Clinical experience and management of adverse events in patients with advanced *ALK*-positive non-small-cell lung cancer receiving alectinib

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Alectinib is a preferred first-line therapy for patients with advanced anaplastic lymphoma kinase (*ALK*)-positive non-small-cell lung cancer (NSCLC) in several national clinical practice guidelines. The randomized, global, phase III ALEX study has demonstrated significant improvement in progression-free survival for alectinib over crizotinib in treatment-naive *ALK*-positive NSCLC. It was also the first study to show clinically meaningful improvement in overall survival for a next-generation ALK tyrosine kinase inhibitor relative to crizotinib. The J-ALEX and ALESIA phase III studies confirmed the clinical benefit of alectinib relative to crizotinib in the first-line *ALK*-positive NSCLC treatment setting in Japanese and Asian patients, respectively. Across these pivotal phase III trials, alectinib had a manageable, well-characterized safety profile. Here, we review the safety and tolerability of long-term alectinib treatment in patients with advanced *ALK*-positive NSCLC and provide guidance for physicians, based on clinical experience, on the management of the most frequently reported adverse events (AEs). Most AEs associated with alectinib can be managed by dose reduction. Some alectinib-related AEs are not yet fully characterized, including myalgia and peripheral oedema and deciphering their underlying mechanism of action could enhance their management. With longer-term follow-up, the safety profile of alectinib continues to remain consistent in the ALEX study, with no new safety signals observed. Safety and tolerability data from the first-line phase III alectinib trials are also consistent with those observed in clinical trials of alectinib in later-line settings. These results add to the weight of evidence recommending alectinib as a preferred therapy for treatment-naive advanced *ALK*-positive NSCLC.

Key words: alectinib, *ALK*-positive NSCLC, clinical experience, safety, tolerability

INTRODUCTION

Anaplastic lymphoma kinase (*ALK*)-positive non-small-cell lung cancer (NSCLC) is a distinct subset of lung cancer that occurs in ∼5% of patients with advanced NSCLC.[1,2] Patients with advanced *ALK*-positive NSCLC are typically younger than those with other types of lung cancer, are often never or light smokers, and tend to present with advanced-stage disease.[3-5] Advanced *ALK*-positive NSCLC follows an aggressive course and patients have a higher prevalence of central nervous system (CNS) metastases compared with other types of NSCLC.[3,6]

ALK tyrosine kinase inhibitors (TKIs) are approved treatments for advanced *ALK*-positive NSCLC, with crizotinib, a multitargeted TKI, and next-generation TKIs (alectinib, ceritinib, brigatinib or lorlatinib) recommended in the first-line setting. Alectinib was approved by the US Food and Drug Administration and the European Medicines Agency in 2017. It is listed as a preferred therapy option in the first-line setting in the European Society for Medical Oncology (ESMO) clinical practice guidelines,[7] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®),[8] and the joint American Society of Clinical Oncology and Ontario Health guidelines.[9] Brigatinib[7-9] and lorlatinib[8] are also listed as preferred therapy options. The randomized phase III ALEX study has demonstrated significant improvement in progression-free survival (PFS) for alectinib over crizotinib in treatment-naive *ALK*-positive NSCLC [stratified hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.32-0.58].[10] It was the first study to show clinically meaningful improvement in overall survival (OS) for a next-generation ALK TKI relative to crizotinib in treatment-naive *ALK*-positive NSCLC, with a 5-year OS rate of 62.5% (95% CI 54.3-70.8) with alectinib versus 45.5% (95% CI 33.6-57.4) with crizotinib.[10] Alectinib also

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effectively protects against and treats CNS metastases in patients with advanced *ALK*-positive NSCLC.[11,12]

Due to the prolonged treatment duration and OS seen in patients treated with alectinib in clinical trials, quality of life for patients in real-world practice is becoming increasingly important. Within this article, we describe the safety and tolerability of long-term alectinib treatment and provide guidance for physicians, based on clinical experience, on the management of adverse events (AEs) reported in patients with advanced *ALK*-positive NSCLC receiving alectinib.

CLINICAL PHARMACOLOGY OF ALECTINIB

Alectinib is a highly selective inhibitor of ALK, which disrupts intracellular signaling pathways involved in tumor cell proliferation and survival.[13] It can penetrate the blood–brain barrier and is active in the CNS.[12,14] Alectinib is a poor substrate for the drug efflux transporter, P-glycoprotein (P-gp), and so is not actively transported out of the brain.[14-16]

The pharmacokinetic (PK) parameters for alectinib and its major active metabolite, M4, have been well characterized in healthy individuals and in patients with *ALK*-positive NSCLC. Alectinib is absorbed with maximum concentrations reached 4-6 h after oral administration under fed conditions.[17] Continuous administration of alectinib 600 mg twice daily (b.i.d.) under fed conditions achieved steady-state concentrations of both alectinib and M4 within 7 days, which remained stable thereafter, with an accumulation ratio about six-fold.[16] The geometric mean volume of distribution at steady-state following intravenous administration of alectinib was 475 l, indicating extensive distribution into tissues.[18] *In vitro* metabolism studies showed that cytochrome P450 (CYP) 3A4 is the main CYP isoenzyme mediating alectinib metabolism to M4 in the liver and is estimated to contribute 40%-50% of alectinib metabolism.[19] Results from dedicated clinical pharmacology studies demonstrated no clinically relevant effect of posaconazole, a potent CYP3A inhibitor, or rifampin, a potent CYP3A inducer, on the combined exposure of alectinib and M4, which are considered the clinically relevant analytes.[20] Nevertheless, appropriate monitoring is recommended for patients taking concomitant strong CYP3A inducers and inhibitors.[15] A human mass balance study confirmed that alectinib and M4 were the main circulating moieties, accounting for 76% of the total radioactivity in plasma, with a metabolite/parent ratio of 0.4.[16] Following oral administration of a single dose of ^{14}C-labeled alectinib to healthy subjects, the majority of radioactivity was excreted in faeces (mean recovery 97.8%) with minimal excretion in urine (mean recovery 0.46%).[18] In faeces, 84% of the dose was excreted as unchanged alectinib and 5.8% as M4.[18] Based on a population PK analysis, the apparent clearance of alectinib was 81.9 l/h following multiple oral doses of alectinib 600 mg in patients with *ALK*-positive NSCLC and the geometric mean of the individual elimination half-life for alectinib was estimated to be 32.5 h.[21]

CLINICAL EXPERIENCE WITH ALECTINIB

Efficacy of alectinib

Three pivotal phase III clinical trials of alectinib have been conducted in patients with *ALK*-positive NSCLC: J-ALEX, ALEX and ALESIA.

The open-label, randomized J-ALEX study compared the efficacy and safety of alectinib, at the approved Japanese dose of 300 mg b.i.d., with that of crizotinib in 207 Japanese patients with ALK inhibitor-naive *ALK*-positive NSCLC, who were chemotherapy-naive or had received one prior chemotherapy regimen.[22,23] As determined by an independent review facility, alectinib significantly prolonged PFS relative to crizotinib (HR 0.37, 95% CI 0.26-0.52; median PFS 34.1 months versus 10.2 months, respectively).[23] OS data were immature at the second interim analysis: median OS was not reached (NR) with alectinib and was 43.7 months with crizotinib (stratified HR 0.80, 99.8799% CI 0.35-1.82, stratified log-rank P = 0.3860).[23] At the final OS analysis of J-ALEX after 5 years of follow-up, median OS was NR in either treatment arm (HR 1.03, 95.0405% CI 0.67-1.58), but these results may have been confounded by the crossover of a high proportion of patients (78.8%) in the crizotinib arm to receive alectinib as a first subsequent anticancer therapy.[24]

In the global ALEX study, 303 patients with advanced *ALK*-positive NSCLC were randomized to receive 600 mg b.i.d. alectinib (globally approved dose) or 250 mg b.i.d. crizotinib as first-line therapy.[10,11,25] At the primary analysis (data cut-off: 9 February 2017), investigator-assessed PFS was significantly longer with alectinib than with crizotinib (HR 0.47, 95% CI 0.34-0.65, $P < 0.001$; median PFS NR versus 11.1 months, respectively).[11] In an updated analysis of the ALEX study (data cut-off: 1 December 2017), median PFS was 34.8 months with alectinib and 10.9 months with crizotinib (HR 0.43, 95% CI 0.32-0.58).[25] Mature PFS data (data cut-off: 30 November 2018) confirmed these earlier analyses, reporting median investigator-assessed PFS of 34.8 months with alectinib and 10.9 months with crizotinib (stratified HR 0.43, 95% CI 0.32-0.58, $P < 0.001$).[10] OS data remain immature at the most recent data cut-off (29 November 2019),[10] with a clinically meaningful 5-year OS rate of 62.5% (95% CI 54.3-70.8) with alectinib versus 45.5% (95% CI 33.6-57.4) with crizotinib.[10]

To assess consistency of the PFS benefit observed in the ALEX study, the randomized ALESIA study compared the efficacy of first-line treatment with alectinib or crizotinib in 187 Asian patients with advanced *ALK*-positive NSCLC.[26] Patients receiving alectinib achieved significantly longer investigator-assessed PFS than those receiving crizotinib (HR 0.22, 95% CI 0.13-0.38, $P < 0.0001$; median PFS NR versus 11.1 months, respectively),[26] confirming the clinical benefit of alectinib reported in the global patient population. Alectinib has demonstrated consistent results in these three phase III trials, which are now translating into real-world clinical practice.[27]

Safety and tolerability of alectinib

The safety profile of alectinib is well characterized and consistent in the 380 patients treated with alectinib across the pivotal phase III studies.[10,11,23,25,26]

Table 1. Safety summary from the ALEX study

Safety population	Primary analysis 9 February 2017[11]		Updated analysis 1 1 December 2017[25]		Updated analysis 2 30 November 2018[40]		Updated analysis 3 29 November 2019[10]	
	Alectinib (n = 152)	Crizotinib (n = 151)	Alectinib (n = 152)	Crizotinib (n = 151)	Alectinib (n = 152)	Crizotinib (n = 151)	Alectinib (n = 152)	Crizotinib (n = 151)
Median treatment duration, months (range)	17.9 (0-29)	10.7 (0-27)	27.0 (0-39)	10.8 (0-37)	27.7	10.8	28.1	10.8
Any grade AEs, *n* (%)	147 (97)	146 (97)	147 (97)	147 (97)	147 (97)	147 (97)	147 (97)	147 (97)
Serious AEs, *n* (%)	43 (28)	44 (29)	46 (30)	46 (31)	54 (36)	48 (32)	59 (39)	48 (32)
Grade 3-5 AEs, *n* (%)	63 (41)	76 (50)	68 (45)	77 (51)	74 (49)	83 (55)	79 (52)	85 (56)
Fatal AEs, *n* (%)	5 (3)	7 (5)	6 (4)	7 (5)	6 (4)	7 (5)	7 (5)	7 (5)
AEs leading to treatment discontinuation, *n* (%)	17 (11)	19 (13)	20 (13)	20 (13)	21 (14)	22 (15)	22 (15)	22 (15)
AEs leading to dose reduction, *n* (%)	24 (16)	31 (21)	25 (16)	31 (21)	29 (19)	30 (20)	31 (20)	30 (20)
AEs leading to dose interruption, *n* (%)	29 (19)	38 (25)	34 (22)	38 (25)	38 (25)	39 (26)	40 (26)	40 (27)

AE, adverse event.

In J-ALEX, 36.9% of alectinib-treated patients experienced grade ≥3 AEs.[23] AEs leading to alectinib dose interruption or withdrawal occurred in 34.0% and 11.7% of patients, respectively. The most common any-grade AEs in the alectinib arm were constipation [39/103 (37.9%)], nasopharyngitis [39/103 (37.9%)], and upper respiratory tract infection [28/103 (27.2%)]; the most frequent grade ≥3 AEs were increased creatine phosphokinase (CPK) and interstitial lung disease [5/103 (4.9%) each]. There were no grade 5 AEs.

At the updated safety analysis of the ALEX study (data cut-off: 29 November 2019), median duration of alectinib treatment was 28.1 months.[10] No new safety signals were observed with longer follow-up and the safety profile of alectinib remained consistent with the primary analysis of the study and with two previous updated analyses (Table 1). Grade ≥3 AEs were observed in 52.0% of alectinib-treated patients. AEs leading to alectinib dose reduction, interruption or discontinuation occurred in 20.4%, 26.3% and 14.5% of patients, respectively. The most common any-grade AEs with alectinib were constipation [56/152 (36.8%)], anaemia [40/152 (26.3%)], fatigue [34/152 (22.4%)], and increased blood bilirubin [33/152 (21.7%)] (Table 2). The most common grade ≥3 AEs in the alectinib arm were anaemia [9/152 (5.9%)], increased aspartate aminotransferase [AST; 8/152 (5.3%)], increased alanine aminotransferase [ALT; 7/152 (4.6%)], and pneumonia [7/152 (4.6%)] (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100612). Seven patients (4.6%) in the alectinib arm died due to grade 5 AEs (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100612).

In ALESIA, grade ≥3 AEs were observed in 29% of alectinib-treated patients.[26] AEs leading to alectinib dose reduction, interruption or discontinuation occurred in 24%, 26% and 7% of patients, respectively. The most common any grade AEs with alectinib were increased blood bilirubin [61/125 (49%)], increased CPK [55/125 (44%)] and increased ALT [52/125 (42%)]. The most common grade ≥3 AEs in the alectinib arm were increased CPK [6/125 (5%)] and weight gain [4/125 (3%)]. Two patients (2%) experienced fatal grade 5 AEs, but these were not considered related to alectinib treatment.

Safety and tolerability data from the phase III first-line alectinib trials are consistent with those observed in clinical trials of alectinib in later-line settings.[28-30] To date, an estimated cumulative total of 72 052 patients have been exposed to alectinib in clinical practice. Most AEs associated with alectinib 600 mg b.i.d. can be managed by dose

Table 2. AEs reported in ≥10% of patients in the alectinib arm (n = 152) of the ALEX study (data cut-off: 29 November 2019)

n (%)	TEAEs						TRAEs
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Any AEs	147 (96.7)	138 (90.8)	112 (73.7)	69 (45.4)	14 (9.2)	7 (4.6)	123 (80.9)
Constipation	56 (36.8)	47 (30.9)	8 (5.3)	1 (0.7)	0	0	42 (27.6)
Liver function abnormalities	52 (34.2)	16 (10.5)	22 (14.5)	12 (7.9)	2 (1.3)	0	45 (29.6)
Anaemia	40 (26.3)	12 (7.9)	19 (12.5)	8 (5.3)	1 (0.7)	0	24 (15.8)
Fatigue	34 (22.4)	28 (18.4)	4 (2.6)	2 (1.3)	0	0	24 (15.8)
Peripheral oedema	29 (19.1)	25 (16.4)	4 (2.6)	0	0	0	16 (10.5)
Myalgia	26 (17.1)	21 (13.8)	5 (3.3)	0	0	0	17 (11.2)
Nausea	25 (16.4)	20 (13.2)	4 (2.6)	1 (0.7)	0	0	12 (7.9)
Diarrhoea	24 (15.8)	18 (11.8)	5 (3.3)	1 (0.7)	0	0	11 (7.2)
Upper respiratory tract infection	21 (13.8)	8 (5.3)	12 (7.9)	1 (0.7)	0	0	0
Rash	21 (13.8)	16 (10.5)	2 (1.3)	2 (1.3)	1 (0.7)	0	16 (10.5)
Arthralgia	20 (13.2)	16 (10.5)	3 (2.0)	1 (0.7)	0	0	6 (3.9)
Back pain	20 (13.2)	12 (7.9)	5 (3.3)	3 (2.0)	0	0	0

AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

reduction in incremental steps of 150 mg b.i.d. based on tolerability.[15,16]

METHODS

The data presented in this article are from the most recent data cut-off of the ALEX study, 29 November 2019. All analyses reported are descriptive and have not been formally tested. Time to onset of the AE of interest was analysed with descriptive statistics. Time to resolution was analysed using Kaplan—Meier methodology within the group of patients that experienced the AE of interest. The probability of a specific AE was analysed with the cumulative incidence by using a competing risk methodology, where the onset of the AE of interest was compared with death from any cause and the end of follow-up.

MANAGEMENT OF AES EXPERIENCED BY PATIENTS RECEIVING ALECTINIB

Myalgia

The mechanism of action of myalgia associated with alectinib treatment is currently unknown. One case report in a patient treated with alectinib suggested an inflammatory muscular mechanism of this event.[31] As myalgia is a subjective AE, patients with the same grade event may experience very different impacts on their quality of life, especially if myalgia occurs daily. In the ALEX study, myalgia was reported in 17.1% (26/152) of patients receiving alectinib, with alectinib-related myalgia in 11.2% (17/152) of patients (Table 3 and Figure 1). The median time to onset of myalgia was 1.1 months [interquartile range (IQR), 0.3-7.8] and the median time to resolution was 8.1 months (IQR, 2.1-39.3). All events of myalgia were mild in severity [grade 1 (80.8%) or 2 (19.2%)]; three patients (11.5%) experienced a single recurrence of the event. The probability of myalgia remained relatively constant over time, at 11.8% at 3 months, 12.5% at 6 months and 13.8% at 12 months.

In our clinical experience, the frequency of myalgia in real-world clinical practice may be lower than that observed in the ALEX study and it typically occurs within the first 2-3 months of alectinib treatment. Patients should be advised, however, of the possibility of myalgia occurring when initiating alectinib treatment and reassured that it can be easily managed. Patients must be followed up regularly to assess the impact of myalgia on their daily lives. In addition, patient's CPK levels should be monitored every 2 weeks during the first month of alectinib treatment and as clinically indicated in symptomatic patients.[15,16] If severe CPK elevations occur (>10 times the upper limit of normal), it is recommended to withhold alectinib and resume at a reduced dose once the event has resolved (Table 4).

Peripheral oedema

The pathophysiology of peripheral oedema associated with alectinib treatment is unknown. Peripheral oedema may occur due to a class effect of ALK TKIs, but it can present differently with alectinib (e.g. only in the legs) than with other ALK TKIs. Peripheral oedema associated with ALK TKIs, in particular crizotinib, has been shown to occur via inhibition of c-MET activity, which is present in normal adult nephrons,[32] although alectinib does not have inhibitory activity against c-MET.[33] In patients who received alectinib in the ALEX study, peripheral oedema was reported in 19.1% (29/152) of patients, with alectinib-related events in 10.5% (16/152) (Table 3 and Figure 1). The median time to onset of event was 2.3 months (IQR, 0.7-9.5) with a median time to resolution of 12.9 months (IQR, 1.1-37.7). All events of peripheral oedema were mild in severity [grade 1 (86.2%) or 2 (13.8%)] and six patients (20.7%) experienced a recurrence. The probability of peripheral oedema increased from 9.9% at 3 months, to 13.8% at 6 months and 15.1% at 12 months.

It is important to exclude other sources of peripheral oedema and, if the source is known, to consider a short course of diuretics (Table 4). Patients receiving alectinib should be advised to use pressure stockings to reduce fatigue in their legs and to minimize the risk of peripheral oedema. In cases of severe peripheral oedema, a dose reduction of alectinib is recommended.

Bradycardia

Lower baseline heart rate may predispose patients to bradycardia. Although the exact mechanism of action of bradycardia associated with alectinib is unknown, there is no evidence that alectinib prolongs the QTc interval or results in clinically relevant changes in cardiac function.[34] In the alectinib arm of the ALEX study, bradycardia occurred in

Table 3. Summary of specific AEs in patients in the alectinib arm (n = 152) of the ALEX study (data cut-off: 29 November 2019)

AE	Patients, *n* (%)	Events, *n*	Median time to onset, (IQR)	Number resolved, *n* (%)	Median time to resolution, (IQR)
Constipation	56 (36.8)	72	0.8 (0.3-1.7)	46 (63.9)	5.2 (1.4-NE)
Liver function abnormalities	52 (34.2)	139	1.8 (1.0-5.6)	114 (82.0)	2.4 (1.0-11.3)
Anaemia	40 (26.3)	51	3.9 (1.8-18.6)	32 (62.7)	6.7 (1.0-NE)
Fatigue	34 (22.4)	42	1.0 (0.4-7.4)	25 (59.5)	4.1 (1.5-NE)
Peripheral oedema	29 (19.1)	36	2.3 (0.7-9.5)	26 (72.2)	12.9 (1.1-37.7)
Myalgia	26 (17.1)	29	1.1 (0.3-7.8)	19 (65.5)	8.1 (2.1-39.3)
Rash	21 (13.8)	34	6.1 (0.5-12.1)	31 (91.2)	1.9 (0.4-4.0)
Bradycardia	13 (8.6)	13	1.0 (1.0-11.1)	5 (38.5)	NE (4.6-NE)
Renal toxicity	4 (2.6)	4	3.4 (1.7-4.1)	3 (75.0)	0.4 (0.2-1.1)

AE, adverse event; IQR, interquartile range; NE, not estimable.

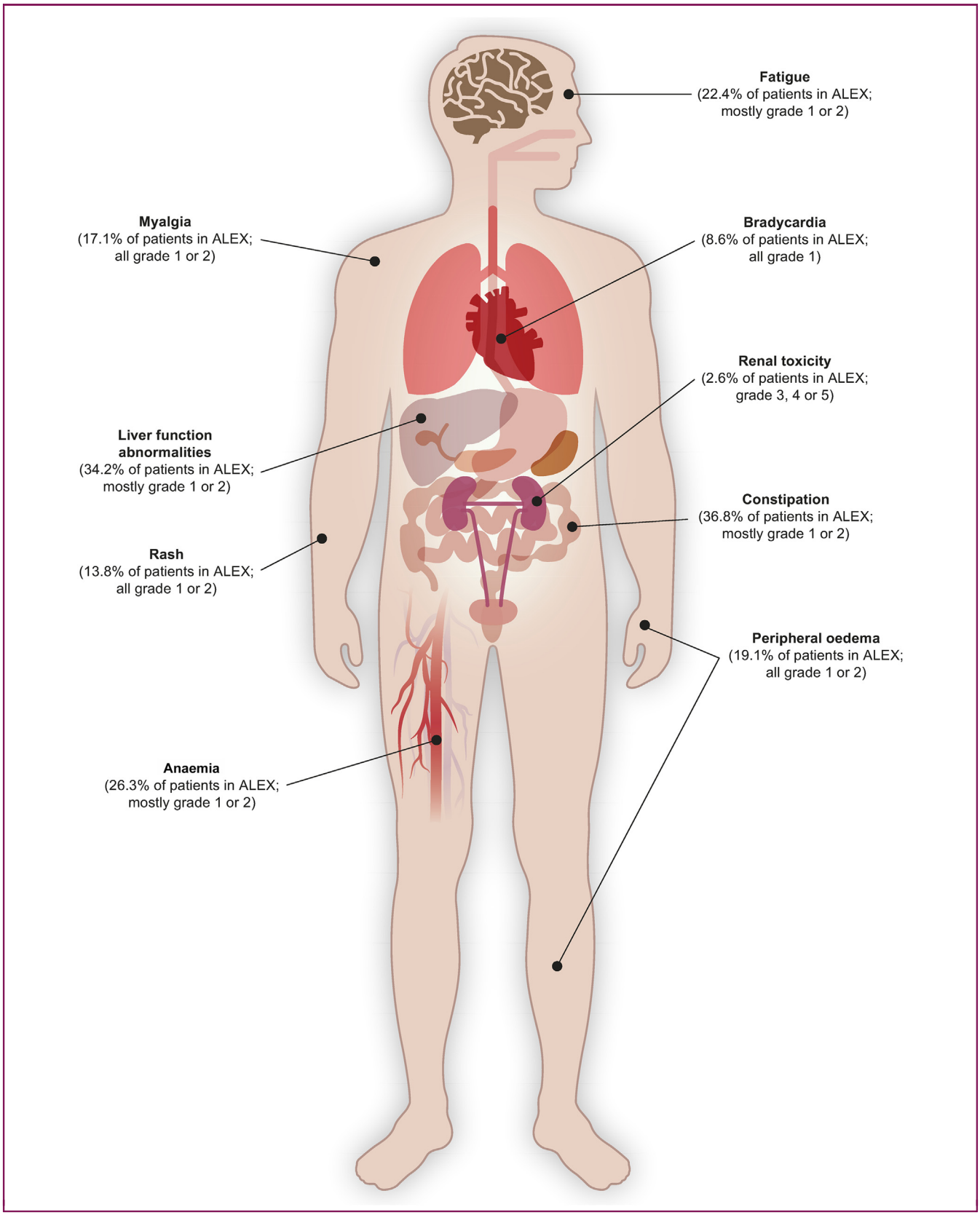

Figure 1. Frequency and severity of specific AEs in patients in the alectinib arm (n = 152) of the ALEX study.
AE, adverse event.

Table 4. Guidance for physicians on the management of AEs in patients receiving alectinib

	Guidance for physicians
Myalgia	• Inform patients of the possibility of myalgia occurring when initiating alectinib treatment and reassure them that it can be easily managed • Advise patients to report any unexplained muscle pain, tenderness or weakness[15,16] • Follow up with patients regularly to assess the impact of myalgia on their daily life, as patients may need to reduce their daily activity, which could be more difficult for younger patients • Assess CPK levels every 2 weeks for the first month of treatment and as clinically indicated in patients reporting symptoms[15,16] • When CPK is elevated to >5 times ULN, temporarily withhold alectinib until recovery to baseline, or to ≤2.5 times ULN, then resume at the same dose[15,16] • When CPK is elevated to >10 times ULN or it is the second occurrence of CPK elevation of >5 times ULN, temporarily withhold alectinib until recovery to baseline or to ≤2.5 times ULN, then resume at a reduced dose[15,16]
Peripheral oedema	• Advise patients to use pressure stockings to reduce fatigue in the legs • Exclude other sources of peripheral oedema (cardiac, liver and renal) • Consider prescribing diuretics as a short-term treatment • If severe, reduce the dose of alectinib
Bradycardia	• Inform patients of the possibility of bradycardia occurring when initiating alectinib treatment and reassure them to not worry about it • Patients with bradycardia while on alectinib treatment are not typically at risk for sudden death but may experience dizziness or syncope • Advise patients that their GP or cardiologist should seek input from their oncologist before reducing the dose of alectinib • Avoid co-medications, such as beta blockers, which may cause bradycardia • Dose modification is not required in case of asymptomatic bradycardia[15,16] • If patients experience symptomatic bradycardia (grade 2/3) or life-threatening (grade 4) events, concomitant medicinal products known to cause bradycardia, as well as antihypertensive medicinal products should be evaluated and the alectinib dose should be adjusted[15,16] ◦ Refer to cardiologist; perform ECG every 1-3 months or refer for Holter monitoring and exclude other possible underlying conditions if patient is symptomatic • Resume alectinib at a reduced dose upon recovery to asymptomatic bradycardia or to a heart rate of ≥60 bpm, with frequent monitoring as clinically indicated[15,16] • Permanently discontinue alectinib if no contributing concomitant medicinal product is identified or in case of recurrence[15,16] • If bradycardia continues, a pacemaker may need to be fitted
Liver function abnormalities	• Review the patient's co-medications and dietary habits • Monitor liver function, including ALT, AST and total bilirubin at baseline, then every 2 weeks during the first 3 months of treatment[15,16] ◦ Thereafter, monitoring should be carried out periodically, since events may occur later than 3 months, with more frequent testing in patients who develop aminotransferase and bilirubin elevations[15,16] • If severe (grade 3/4), withhold and resume at a reduced dose of alectinib, or permanently discontinue[15,16] • If severe, conduct further investigations for the presence of liver metastases
Anaemia	• Exclude other sources of anaemia, in particular, abundant menstrual bleeding and iron metabolism disturbances • If severe, reduce the dose of alectinib, consider a blood transfusion when clinically indicated[37] and screen for haemolysis • Advise patients to report if they develop any signs or symptoms of haemolytic anaemia, such as jaundice, weakness or dizziness, or shortness of breath[16] • Alectinib SmPC[15] ◦ If haemoglobin concentration is <10 g/dl and haemolytic anaemia is suspected, withhold alectinib and appropriate laboratory testing should be initiated ◦ If haemolytic anaemia is confirmed, resume alectinib at a reduced dose upon resolution • Alectinib prescribing information[16] ◦ If haemolytic anaemia is suspected, withhold alectinib ◦ If haemolytic anaemia is confirmed, consider resuming alectinib at a reduced dose upon resolution or permanently discontinue
Fatigue	• Exclude other sources of fatigue, such as low iron metabolism as a predisposing factor for anaemia or monitor weight • If severe, reduce the dose of alectinib
Constipation	• Follow current ESMO Clinical Practice guidelines on constipation in advanced cancer[38] • Consider dietary recommendations or laxative treatment
Renal toxicity	• Check if patients are drinking enough fluids • Carefully assess concomitant medications for their effects on renal function, such as nonsteroidal anti-inflammatory drugs • Consider carrying out CT without contrast for efficacy assessments • Alectinib SmPC[15] ◦ No dose adjustment of alectinib is required in patients with mild or moderate renal impairment ◦ Alectinib has not been studied in patients with severe renal impairment; since alectinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment • Alectinib prescribing information[16] ◦ Withhold alectinib for grade 3 renal toxicity until recovery to ≤1.5 times ULN, then resume at a reduced dose ◦ Permanently discontinue alectinib for grade 4 renal toxicity
Rash	• Advise patients to avoid direct or prolonged sun exposure while taking alectinib and for ≥7 days after discontinuation of treatment[15,16] • Advise patients to also use a broad-spectrum UVA/UVB sunscreen and lip balm (SPF ≥50) to help protect against potential sunburn[15,16]

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beats per minute; CPK, creatine phosphokinase; CT, computed tomography; ECG, electrocardiogram; ESMO, European Society of Medical Oncology; GP, general practitioner; SmPC, summary of product characteristics; SPF, sun protection factor; ULN, upper limit of normal.

8.6% (13/152) of patients, with alectinib-related events reported in 7.2% (11/152) of patients (Table 3 and Figure 1). The median time to onset of bradycardia was 1.0 month (IQR, 1.0-11.1). The median time to resolution was not estimable (NE) (IQR, 4.6-NE). All reported events were grade 1 in severity (100%) and no patients experienced recurrence of bradycardia. The probability of bradycardia remained roughly constant over time from 5.3% at 3 months, to 5.9% at 6 months and 6.6% at 12 months.

In our clinical experience, a higher frequency of bradycardia may be observed in real-world clinical practice than was recorded in the ALEX study. Patients must be informed about the potential for bradycardia to occur when initiating alectinib treatment and advised that they may experience dizziness or syncope. These patients are not typically at risk for sudden death, but all patients with symptomatic (grade 2/3) or life-threatening (grade 4) bradycardia should be referred to a cardiologist. Moreover, concomitant therapies and antihypertensive medications known to cause bradycardia should be avoided and the dose of alectinib reduced until symptoms have resolved (Table 4). If bradycardia continues, despite alectinib dose adjustment, then the patient may ultimately need to be fitted with a pacemaker.

Liver function abnormalities

Hepatic toxicity is commonly observed with ALK TKIs.[35] In patients who received alectinib in the ALEX study, the range of liver function abnormalities reported included increased blood bilirubin, increased ALT, increased AST, increased conjugated bilirubin, increased unconjugated blood bilirubin and increased γ-glutamyltransferase. Liver function abnormalities occurred in 34.2% (52/152) of patients, with alectinib-related events reported in 29.6% (45/152) (Table 3 and Figure 1). The median time to onset of event was 1.8 months (IQR, 1.0-5.6) and the median time to resolution was 2.4 months (IQR, 1.0-11.3). Of the events reported, the majority were mild in severity [grade 1 (30.8%) or 2 (42.3%)]; however, grade 3 and 4 events occurred at a frequency of 23.1% and 3.8%, respectively. Most patients experienced recurrence of liver function abnormalities [63.5% (33/52)], with 23.1% (12/52) of patients having more than two recurrences. The probability of liver function abnormalities increased over time, from 20.4% at 3 months, to 26.3% at 6 months and 28.3% at 12 months.

The clinical management of patients with liver function abnormalities should include a review of the patient's concomitant medications and dietary habits. Patient's liver function must be monitored at baseline, then every 2 weeks during the first 3 months of alectinib treatment. In cases of severe liver function abnormalities (grade 3/4), alectinib should be withheld and resumed at a reduced dose or permanently discontinued; investigations for the presence of liver metastases are recommended at this stage (Table 4).

Anaemia

Anaemia may be related to the pathology of the disease and can cluster with both fatigue and myalgia. Alectinib has been found to induce red blood cell membrane abnormalities that could potentially lead to anaemia via an ALK-independent mechanism.[36] Anaemia occurred at a frequency of 26.3% (40/152) in patients receiving alectinib in the ALEX study, with alectinib-related events reported in 15.8% (24/152) of patients (Table 3). The median time to onset of anaemia was 3.9 months (IQR, 1.8-18.6), with a median time to resolution of 6.7 months (IQR, 1.0-NE). The majority of reported events were mild in severity [grade 1 (30.0%) or 2 (47.5%)] with eight grade 3 events (20%) and one grade 4 event (2.5%). Seven patients (17.5%) experienced recurrence, with one patient (2.5%) having more than two recurrences. The probability of anaemia increased over time, from 10.5% at 3 months, to 14.5% at 6 months and 17.8% at 12 months.

Physicians should aim to exclude other sources of anaemia and to carefully monitor the patient's iron metabolism. In cases of severe anaemia, a dose reduction of alectinib is recommended and a blood transfusion should be considered when clinically indicated[37] (Table 4). Haemolytic anaemia has also been reported with alectinib, including cases associated with a negative direct antiglobulin test result.[16] If haemolytic anaemia is suspected, alectinib should be withheld and appropriate laboratory testing should be initiated.[15,16] Upon resolution, alectinib can be resumed at a reduced dose.

Fatigue

Fatigue is a subjective AE and may be related to myalgia or possibly anaemia. In the alectinib arm of the ALEX study, 22.4% (34/152) of patients experienced fatigue, with alectinib-related events reported in 15.8% (24/152) of patients (Table 3 and Figure 1). The median time to onset was 1.0 month (IQR, 0.4-7.4), with a median time to resolution of 4.1 months (IQR, 1.5-NE). The majority of events were mild in severity [grade 1 (82.4%) or 2 (11.8%)] and only two grade 3 fatigue events (5.9%) were reported. Six patients (17.6%) experienced recurrence. The probability of fatigue increased slightly over time, from 13.8% at 3 months, to 16.4% at 6 months and 17.1% at 12 months.

Fatigue is rarely observed in isolation and is not usually a major issue for patients treated with alectinib in clinical practice (typically grade 1). Physicians should aim to exclude other sources of fatigue and to check the patient's iron metabolism as a predisposing factor for anaemia and monitor their weight (Table 4). A reduction in the dose of alectinib is recommended in cases of severe fatigue.

Constipation

Constipation is a common problem in patients with advanced cancer,[38] and may be related to comorbidities and concomitant medications. In the alectinib arm of the ALEX study, constipation was the most frequently reported AE, occurring in 36.8% (56/152) of patients, with alectinib-related events reported in 27.6% (42/152) of patients (Table 3 and Figure 1). Constipation tended to occur quickly after initiation of alectinib and to persist throughout treatment, with a median time to onset of 0.8 months (IQR,

0.3-1.7) and a median time to resolution of 5.2 months (IQR, 1.4-NE). Of the events reported, most were mild in severity [grade 1 (83.9%) or 2 (14.3%)] and only one patient experienced a grade 3 event (1.8%). Eleven patients (19.6%) experienced a recurrence of constipation, with one patient (1.8%) having more than two recurrences. The probability of constipation remained constant over time, at 30.3% at 3 months, 31.6% at 6 months and 32.9% at 12 months.

The frequency of constipation in clinical practice may be lower than that observed in the ALEX study and therefore is not a major issue for patients treated with alectinib (events are typically grade 1). Physicians are encouraged to consult the current ESMO clinical practice guidelines on constipation in advanced cancer[38] for specific recommendations on how to manage their patients and to consider dietary advice or use of laxatives (Table 4).

Renal toxicity

Alectinib-induced renal toxicity is rare in clinical practice and typically occurs as a gradual decrease in kidney function. Comparison with baseline measurements may therefore be needed to observe its progressive effects. It is also important to determine the definition of renal toxicity, whether that is a mild or moderate change in creatinine clearance or acute kidney failure. Data with crizotinib suggest that creatinine-measured renal clearance may not adequately reflect kidney function due to an effect of crizotinib on creatinine secretion.[39] Other methods of glomerular filtration rate, such as inulin clearance, may need to be considered. Other causes of renal toxicity should also be carefully reviewed, such as computerized tomography (CT) contrast agents, other concomitant medications (such as nonsteroidal anti-inflammatory drugs) and previous history of platinum-based chemotherapy. Renal toxicity occurred in 2.6% (4/152) of patients who received alectinib in the ALEX study, with alectinib-related events reported in 2.0% (3/152) of patients (Table 3 and Figure 1). The median time to onset was 3.4 months (IQR, 1.7-4.1), with a median time to resolution of 0.4 months (IQR, 0.2-1.1). Of the events reported, two were grade 3 (50%) and one was grade 4 (25%); none of the patients experienced recurrence of the event. A fatal grade 5 event of acute kidney injury occurred in one patient (25%) on study day 14. The probability of renal toxicity remained constant at 2.6% from month 6 onwards.

As an initial step, check that patients are drinking sufficient water and carefully assess concomitant medications. No dose adjustment of alectinib is needed in patients with mild or moderate renal impairment (Table 4). In cases of severe renal toxicity (grade 3), alectinib should be withheld and resumed at a reduced dose; alectinib should be permanently discontinued in patients with grade 4 renal toxicity.[16]

Rash

Alectinib-induced hypersensitivity reactions presenting as a skin rash are listed as 'very common' in the alectinib summary of product characteristics.[15] Rash occurred in 13.8% (21/152) of patients receiving alectinib within the ALEX study, with alectinib-related events reported in 10.5% (16/152) of patients (Table 3). The median time to onset of rash was the longest of all the AEs studied, at 6.1 months (IQR, 0.5-12.1), and the median time to resolution was 1.9 months (IQR, 0.4-4.0). Of the events reported, the majority were mild in severity [grade 1 (76.2%) or 2 (9.5%)] with two grade 3 events (9.5%) and one grade 4 event (4.8%). Seven patients experienced recurrence (33.3%), with two patients (9.5%) having more than two recurrences. The probability of rash increased slightly over time, from 6.6% at 3 months, to 9.2% at 9 months and 9.9% at 12 months.

Patients should be advised to avoid direct or prolonged sun exposure while taking alectinib and to apply broad-spectrum UVA/UVB sunscreen to help protect against sunburn (Table 4).

Other AEs of potential medical importance

Some rare (<2% of patients) treatment-related AEs of potential medical importance were reported in the alectinib arm of the ALEX study. These included blurred vision and pneumonia [both 2/152 (1.3%)], as well as visual impairment, reduced visual acuity, alopecia, atrial fibrillation, atrioventricular block, palpitations, pneumonitis and respiratory failure [all 1/152 (0.7%)].

CONCLUSIONS

Alectinib is well tolerated and has a well-characterized, manageable safety profile over a prolonged treatment duration of up to 5 years.[10] Our collective experience based on real-world clinical practice is generally similar to that observed in the ALEX study, though the clinical experiences of other physicians may vary depending on the patient population. A controlled clinical trial is still the best method to evaluate the incidence of AEs across different patient populations. AEs associated with alectinib are typically managed by a dose reduction of alectinib. Several toxicities associated with alectinib are not yet fully characterized, including myalgia, peripheral oedema and bradycardia, and understanding the mechanisms of action responsible would further aid their management. Myalgia and peripheral oedema are among the most debilitating AEs for patients, given their impact on quality of life, whereas the most challenging AEs to manage from a physician's perspective are bradycardia, as it is unpredictable, and peripheral oedema, as it is difficult to manage and associated with comorbidities.

Overall, the safety profile of alectinib continues to remain consistent and manageable in the global ALEX study, with no new safety signals observed after up to 5 years of follow-up. Safety and tolerability data from the first-line treatment phase III alectinib trials are also consistent with those observed in clinical trials of alectinib in later-line settings.

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DATA SHARING

For eligible studies qualified researchers may request access to individual patient level clinical data through a data request platform. At the time of writing this request platform is Vivli. https://vivli.org/ourmember/roche/. For up to date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymised records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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