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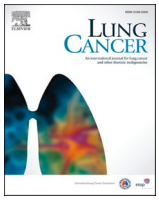

Review article

A pragmatic guide for management of adverse events associated with lorlatinib

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ABSTRACT

Lorlatinib is a brain-penetrant, third-generation tyrosine kinase inhibitor (TKI) indicated for the treatment of anaplastic lymphoma kinase (*ALK*)-positive metastatic non-small cell lung cancer (NSCLC). In clinical trials, lorlatinib has shown durable efficacy and a manageable safety profile in treatment-naive patients and in those who have experienced progression while receiving first- and/or second-generation ALK TKIs. Lorlatinib has a distinct safety profile from other ALK TKIs, including hyperlipidemia and central nervous system effects. Clinical trial data showed that most adverse events (AEs) can be managed effectively or reversed with dose modifications (such as dose interruptions or reductions) or with concomitant medications without compromising clinical efficacy or quality of life for patients. A pragmatic approach to managing AEs related to lorlatinib is required. We present patient-focused recommendations for the evaluation and management of select AEs associated with lorlatinib developed by clinicians and nurses with extensive lorlatinib expertise in routine clinical practice. The recommendations follow the general framework of "prepare, monitor, manage, reassess" to streamline AE management and assist in practical, actionable, and personalized patient care.

1. Introduction

Anaplastic lymphoma kinase (*ALK*) gene rearrangements are present in 2% to 7% of the non-small cell lung cancer (NSCLC) patient population [1–3]. Identification of *ALK* gene rearrangements in NSCLC is clinically important as tumors harboring this genomic alteration are highly sensitive to ALK tyrosine kinase inhibitors (TKIs) [3]. According to international guidelines, the preferred first-line treatment option for patients with *ALK*-positive metastatic NSCLC includes second-generation ALK TKIs, alectinib or brigatinib, or the third-generation ALK TKI, lorlatinib [4,5].

Lorlatinib is a highly potent, brain-penetrant TKI that targets ALK and ROS1 and has broad-spectrum potency against most known acquired ALK kinase domain mutations (eg, *ALK* G1202R) [6,7]. Preclinical activity was also observed against TYK1, FER, FPS, TRKA/B/C, FAK, FAK2, and ACK at higher concentrations than that required to inhibit ALK [6,8]. It is indicated in Australia, Canada, the European Union, Japan, the United States, and other countries for the treatment of adult patients with *ALK*-positive metastatic NSCLC based on the results from a phase 1/2 study (NCT01970865) and the phase 3 CROWN study

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; PFS, progression-free survival; QOL, quality of life; TKI, tyrosine kinase inhibitor.

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(NCT03052608) [9–17]. In the phase 1/2 study, lorlatinib showed overall and intracranial activity in previously treated patients with *ALK*-positive advanced NSCLC [9,10]. The updated analysis of the first-line CROWN study after 36.7 months of follow-up confirmed the long-term benefit of lorlatinib over crizotinib (median progression-free survival [PFS]: not reached vs 9.3 months; hazard ratio, 0.27; 95% CI, 0.18–0.39) [12].

2. Lorlatinib safety profile

The safety profile of lorlatinib is distinct and includes hyperlipidemia, edema, weight gain, peripheral neuropathy, and central nervous system (CNS) events (Table 1) [9–13,18,19]. Some of the AEs associated with lorlatinib have also been reported with other ALK TKIs, including gastrointestinal distress (eg, nausea, vomiting, diarrhea, and constipation) and fatigue [6,12,13,20,21]. Gastrointestinal effects are relatively less common with lorlatinib than with some other ALK TKIs. While real-world lorlatinib data is currently limited to second-line or subsequent lines, the safety profile has been consistent with prior clinical studies with no new safety signals reported. Some real-world studies reported lower AE incidences than clinical trials, which may be a result of differences in monitoring and reporting or early dose modifications for management [22–25].

In the updated CROWN analysis, grade 3/4 adverse events (AEs) occurred in 76% of patients (113/149) treated with lorlatinib, most frequently due to elevations in lipid levels (hypertriglyceridemia in 23% [34/149] and hypercholesterolemia in 19% [29/149] of patients) as well as weight gain (20% [30/149] of patients). In the lorlatinib arm, AEs led to temporary discontinuation in 56%, dose reduction in 21%, and permanent discontinuation in 7% of patients. The most common reason for dose reduction was edema (7% [10/149]), and the most common reason for permanent discontinuation was attributed to cognitive effects (1% [2/149]) [12]. While direct comparisons are not possible, similar rates of dose modifications were observed for alectinib and brigatinib in the latest analyses of the phase 3 ALEX and ALTA-1L studies, respectively [20,21]. In ALEX, AEs led to dose interruption in 26.3%, dose reduction in 20.4%, and permanent discontinuation in 14.5% of patients who received first-line alectinib [20]. In ALTA-1L, AEs led to dose interruption in 72%, dose reduction in 44%, and permanent discontinuation in 13% of patients who received brigatinib [21].

In clinical trials, most lorlatinib AEs, including laboratory abnormalities, were effectively managed or reversed with dose modifications, which include dose reductions and/or interruptions or the addition of concomitant medications [9–12,18,26]. Lorlatinib dose modifications can readily be implemented as they have not been shown to have a negative effect on PFS or intracranial time to progression and can preserve quality of life (QOL) for patients [27–29].

Table 1
Select adverse events in patients treated with first-line lorlatinib in phase 3 CROWN study [12].

Adverse drug reactions	Lorlatinib (n = 149)	
	Any grade	Grade 3/4
Hypercholesterolemia	72%	19%
Hypertriglyceridemia	66%	23%
Edema	56%	4%
Weight increase	44%	20%
Peripheral neuropathy	40%	1%
Cognitive effects	26%	3%
Arthralgia	26%	1%
Hypertension	22%	11%
Diarrhea	22%	1%
Fatigue	19%[a]	1%[a]
Mood effects	17%	1%
Speech effects	5%	1%
Psychotic effects	5%	1%

[a] Data from interim analysis published in Shaw AT, et al. NEJM 2020 [11].

While lorlatinib AEs have been effectively managed in clinical trials, allowing patients to derive maximal benefit from lorlatinib [11,12,26,27], there is a need to develop pragmatic recommendations to manage lorlatinib AEs in routine clinical practice. This article aims to transfer the clinical trial and real-world experience of a panel of thoracic oncology experts familiar with lorlatinib administration in routine clinical practice to enable all physicians to maximize benefit from lorlatinib while preserving patient QOL.

3. General principles of a pragmatic guide to AE management with lorlatinib

A general schema for the management of non-laboratory AEs is described in Fig. 1. The first step is to preemptively inform and *prepare* patients and caregivers about what to expect while taking lorlatinib, including the range and likelihood of AEs and the frequency of evaluations. Providers should also familiarize themselves with the range of AEs that can potentially occur with lorlatinib [11,18] and the general time frame in which each AE could develop (Fig. 2) [10,12,13,18,27]. Open communication between healthcare provider and patient/caregiver should be emphasized while preparing for treatment with lorlatinib, as prompt AE recognition and reporting by patients is necessary for optimal management [18,30]. For instance, the patients and caregivers should be advised prior to treatment initiation of the broad spectrum of CNS AEs that may occur with lorlatinib; they should be encouraged to be mindful of and disclose any symptoms, regardless of severity, to their healthcare provider to ensure proper immediate management [18]. Healthcare providers, patients, and caregivers should be assured that the vast majority of lorlatinib side effects can be managed with dose modification [11,12].

Prior to initiating lorlatinib, patients should undergo several assessments, including a neurological evaluation and magnetic resonance imaging of the brain [30]. Cardiovascular function should be tested via electrocardiogram at baseline and periodically throughout treatment. Blood pressure should be assessed and controlled at baseline, after the first 2 weeks, and then periodically throughout treatment, taking into consideration the patient's overall health. As hyperglycemia can occur, fasting serum glucose should be assessed at baseline and periodically throughout treatment. Hyperlipidemia is a common AE associated with lorlatinib, so serum cholesterol and triglycerides should be monitored before treatment initiation, after 1–2 months, and then periodically throughout treatment [13].

Additionally at baseline, patients should be assessed for comorbidities and concurrent medications that may cause or exacerbate symptoms of lorlatinib-associated toxicity [13,30]. While mild to moderate renal impairment does not necessitate a reduced dose, severe renal impairment (creatinine clearance of 15 to <30 mL/min) requires dose reduction from 100 mg to 75 mg once daily [13]. Concurrent medications should be discussed to prevent any potential drug interactions. Lorlatinib is contraindicated in combination with strong CYP3A inducers, which decrease the plasma concentration and subsequently potentially efficacy of lorlatinib [13,31]. If moderate CYP3A inducers cannot be avoided, the lorlatinib dose may be increased [13,32]. Conversely, strong CYP3A inhibitors increase lorlatinib plasma concentration and may increase the incidence and severity of AEs; therefore, if concomitant use is unavoidable, lorlatinib should be reduced to 75 mg once daily [13].

The recommended starting dose of lorlatinib is 100 mg once daily [13]. Once lorlatinib has been initiated, patients should be *monitored* for AEs commonly associated with lorlatinib at each follow-up visit [30,32]. Toxicities that should be monitored and reported by patients in between clinic visits include cognitive and memory changes, hallucinations, alterations in speech, and peripheral neuropathy. At clinic visits, weight changes, hypertension, and hyperlipidemia can be further assessed. Monitoring should focus not only on the presence of AEs but also on severity. There is future potential for adjunctive telemonitoring

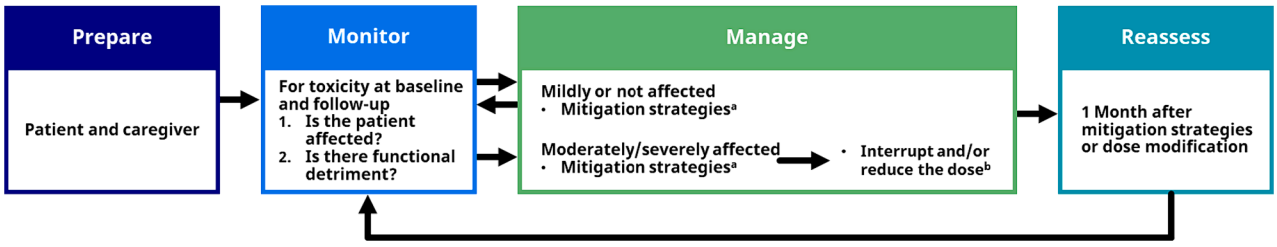


Fig. 1. General management of lorlatinib toxicities: prepare, monitor, manage, reassess. [a]See Fig. 3A and B and Table 2 for details. [b]Interrupt refers to a temporary dose interruption. Reduce refers to dose reduction.

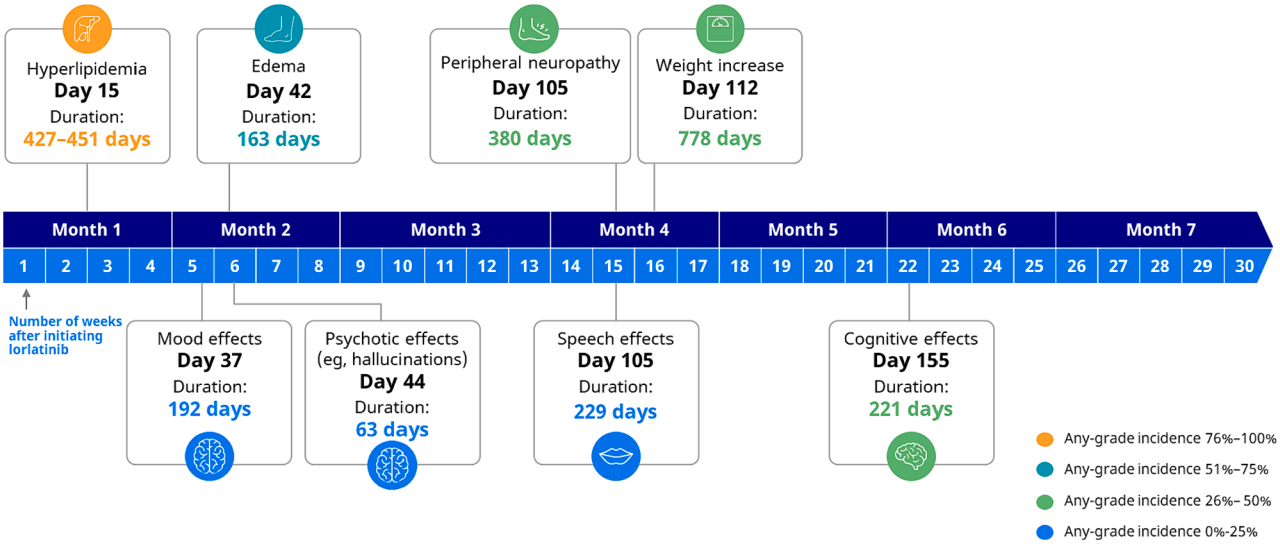


Fig. 2. Typical timeline of lorlatinib select adverse events.[a] [a]The values listed here represent median time to first occurrence for each AE. There is a distribution in which some may occur earlier or later than these median values.[12–14,18,27].

strategies to aid monitoring and rapid reporting of toxicities.

Within the clinical trials, Common Terminology Criteria for Adverse Events (CTCAE) grades were used to measure severity [9–12]. From a pragmatic standpoint, the monitoring of non-laboratory AEs should focus on two key aspects: (1) how much does the specific AE affect the patient and (2) how functionally detrimental is the specific AE? The degree that the patient is affected by the AE is subjective and based on baseline function, daily lifestyle, and activities. Functional detriment is more objective and can be measured by assessing specific key functions (eg, inability to speak or think properly, ability to button shirts). The greater the degree to which the patient experiences bothersome symptoms and functional detriment, the greater the likelihood that mitigation strategies and/or dose modifications will be needed.

If AEs arise during monitoring, the next step is *management*. For symptoms that are either not bothersome or only mildly bothersome (and that minimally affect function, if at all), mitigation strategies rather than dose reduction or temporary dose interruption are generally emphasized (Table 2). For CNS AEs, dose modifications are also recommended for mildly or severely bothersome symptoms. Mitigation strategies, including lifestyle modifications and/or pharmacological interventions, can be implemented concurrently. Dose modification can include a temporary dose interruption, dose reduction, or both. It is rare to require permanent discontinuation [18,32].

When dose reduction is appropriate, the initial starting dose of lorlatinib of 100 mg daily can be reduced to 75 mg daily dose, with a subsequent drop by 25 mg [13]. A low threshold should be used to initiate dose reductions, especially given the preserved clinical efficacy of reduced doses of lorlatinib [27]. Although the general recommendation is that lorlatinib should be discontinued instead of decreasing the dose to 25 mg daily [13], anecdotally, some patients still maintained disease control with a 25-mg daily dose of lorlatinib. Pragmatically, there may be specific occasions where oncologists prefer to start at a dose lower than 100 mg with consideration of escalating to 100 mg in the absence of significant toxicities; this management guide recognizes this approach but is agnostic to the merits of such an approach.

All patients should be *reassessed* at each follow-up visit [18,30,32]. Patients who experienced AEs and required dose modification should be *reassessed* at least monthly until symptoms improve. Once stabilized, a 3-month follow-up is recommended. For non–laboratory-based AEs that require dose reductions, mitigation strategies should continue if symptoms remain moderately or severely bothersome, and the dose may be further reduced if symptoms persist. If symptoms improve, the lorlatinib dose should be maintained or, based on the provider's clinical judgment, potentially increased if the mitigation strategies appear to be working well, or if disease control is compromised. Dose re-escalation is rarely implemented unless the lorlatinib daily dose is $\leq$75 mg, and doses should never be >100 mg per day [13]. For non–laboratory-based AEs that require dose interruption, the temporary pause should continue until AE symptoms improve to the point that the patient is only mildly bothered/functionally affected (or not bothered at all/regained function). Typically, this takes up to several weeks, and reviewing for toxicity improvement should be performed approximately biweekly during dose interruption.

CNS AEs can be difficult to assess and bothersome to manage. To amend the management described in a post hoc analysis of CROWN [27], CNS toxicities that are bothersome to the patient should be managed by implementing temporary dose interruption of lorlatinib. Once symptoms improve, restarting the patient on a reduced dose may

Table 2
Mitigation strategies for select adverse events.

Adverse event	Non-pharmacological mitigation strategies	Pharmacological mitigation strategies
Hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) Elevated lipid levels: total cholesterol ULN-500 mg/dL (12.93 mmol/L) or triglycerides 150–1000 mg/dL (1.71–11.29 mmol/L) [38] Severely elevated lipid levels (life-threatening per CTCAE criteria): total cholesterol >500 mg/dL (12.93 mmol/L) or triglycerides >1000 mg/dL (11.29 mmol/L) [38]	Although dietary changes may be used, typically hyperlipidemia requires pharmacological strategies.	Statins: choose one of pitavastatin (2 mg orally once daily), pravastatin (40 mg orally once daily), or rosuvastatin (5–10 mg orally once daily for moderate-intensity therapy or 20–40 mg orally once daily for high-intensity therapy) [18,32,47].[a] Ezetimibe: the addition of ezetimibe is recommended if the maximum statin dose inadequately controls hyperlipidemia [18,30,47]. Fibrates/fish oil: If triglycerides remain >500 mg/dL (5.65 mmol/L), despite maximum statin doses, the addition of fibrates/fish oils is encouraged [18,30,47].[a] PCSK9 inhibitors are an alternative lipid-lowering medication that may be considered for patients who are statin intolerant [33,34]. If a patient is statin intolerant or there is a lack of response to maximum lipid-lowering therapies, the patient should be referred to cardiovascular or lipid clinics. Triglyceride levels >1000 mg/dL (11.29 mmol/L) are associated with acute pancreatitis, which is diagnosed when 2 of 3 characteristics are present: abdominal pain, increased pancreatic enzymes >3 times the upper limit of normal, and imaging evidence of acute pancreatitis. Management is based on the severity of acute pancreatitis, but initial treatment may range from conservative treatment with intravenous fluids, bowel rest, and pain control to admission to the intensive care unit. Long-term treatment focuses on lowering triglyceride levels [36,37].
Edema	Rule out alternative causes, such as cardiac (heart failure), renal, and thyroid causes. Examples of helpful interventions include compression garments, raising the affected area above the heart, increased exercise, limiting dietary salt, physiotherapy, and lymphedema massage.	There is limited scientific evidence to support the use of diuretics. However, based on the authors' clinical experience in managing edemas, diuretics can be used as an option for management. If persistent, healthcare providers are encouraged to consult with the respective specialists (ie, cardiologist, endocrinologist, etc.) to consider other causes and to help identify other solutions.
Weight gain	Food intake counseling, dietary advice, and/or the addition of exercise can be helpful.	Currently there is no data on the use of semaglutide or other incretins in the management of lorlatinib-induced weight gain. Any use of semaglutide or other incretins should be per approved indications and under expert physician management of the potential side effects.
Peripheral neuropathy	A night splint may improve carpal tunnel syndrome. Peripheral neuropathy associated with edema (particularly in the upper extremities) may respond to compression garments, raising the affected area above the heart, increased exercise, limiting dietary salt, physiotherapy, and lymphedema drainage/massage.	Treatments: vitamin B_1 and vitamin B_6 and medications (gabapentin or pregabalin) may provide symptom relief.
CNS effects (cognitive, mood, speech, psychotic)	Potentially manage other causes of neurocognitive and psychiatric impairment and visit a specialist (eg, neurologist, psychiatrist). Strategies to minimize the impact of CNS effects such as setting reminders, mindfulness, meditation, and cognitive behavioral therapy may be useful.	Lorlatinib early dose interruption and dose reduction. If severe, refractory CNS effects occur, consider a psychiatrist for pharmacological management (antipsychotics, antidepressants).

CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; CYP, cytochrome P450; ULN, upper limit of normal.
[a] Pitavastatin, pravastatin, or rosuvastatin are suggested for use with lorlatinib based on their low involvement with specific cytochrome P450 enzymes that interact with lorlatinib (eg, CYP3A4). Fenofibrate has the least involvement with CYP enzymes, followed by fish oils and nicotinic acid.

be preferred. Dose escalation after the resolution of symptoms is not recommended. For hyperlipidemia, as a laboratory AE is not associated with symptoms, pharmacological mitigation strategies rather than dose modification are the preferred approach.

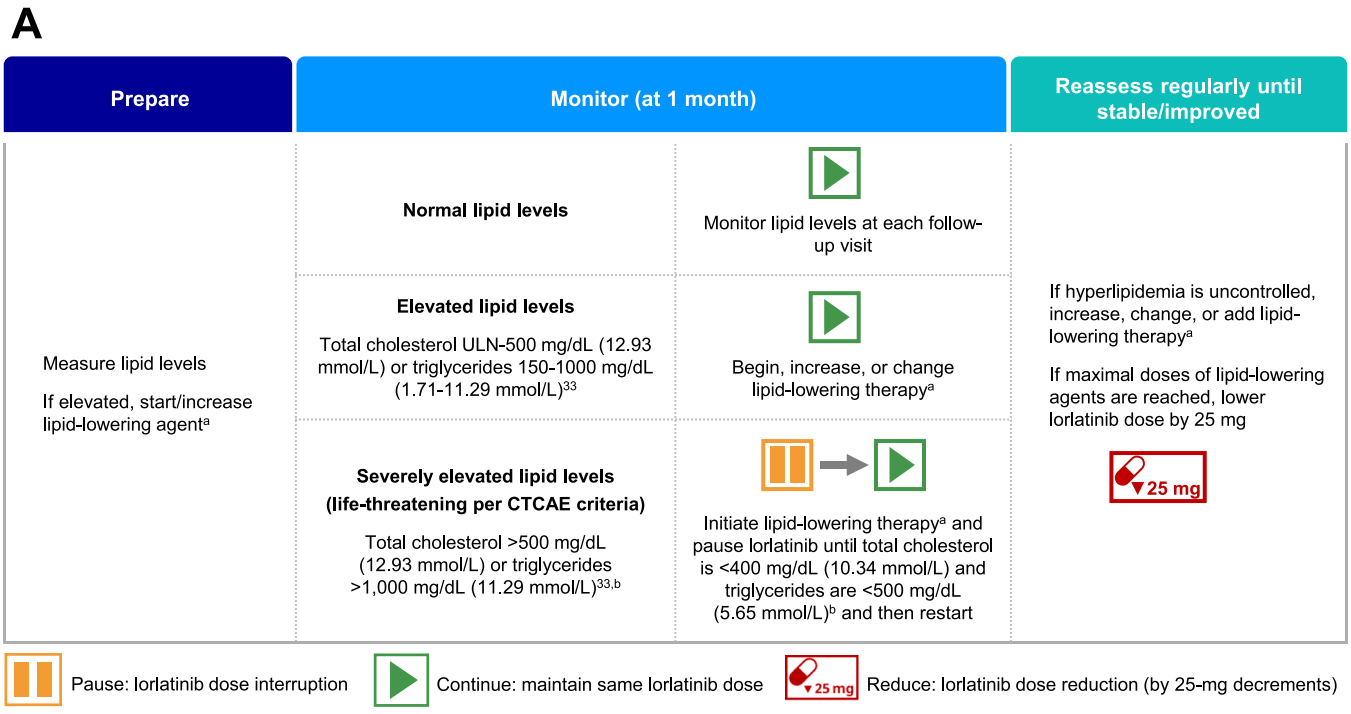
4. Detailed management plans for specific AEs

4.1. Hyperlipidemia

Hyperlipidemia is the most common AE reported with lorlatinib and can occur within the first few weeks of treatment; however, this is typically an asymptomatic laboratory abnormality [18]. Hyperlipidemia occurs with a median time to onset of 15 days and persists for over 400 days (Fig. 2) [13,14,18]. In the updated CROWN analysis (36.7 months of follow-up), hypercholesterolemia was observed in 72% of patients and hypertriglyceridemia in 66% of patients (Table 1). Although most (68%) treatment-emergent hyperlipidemia events in the lorlatinib clinical trials required at least one lipid-lowering agent and 9% required concomitant medication plus additional interventions, hyperlipidemia is very manageable and rarely results in dose interruptions (19/237) or

reductions (9/237). In this updated CROWN analysis, an increased incidence of cardiac events was not observed with lorlatinib treatment compared with crizotinib treatment, even in the presence of hyperlipidemia. In fact, there was no increase in incidence or severity of cardiovascular events during the 18 months of follow-up after the interim CROWN analysis. Dose reductions due to hypertriglyceridemia or hypercholesterolemia were reported in 4% and 2% of patients, respectively, and hyperlipidemia led to permanent discontinuation in 1% of patients [12].

Hyperlipidemia management strategies are outlined in Fig. 3A. To prepare for treatment with lorlatinib, blood lipids and population-



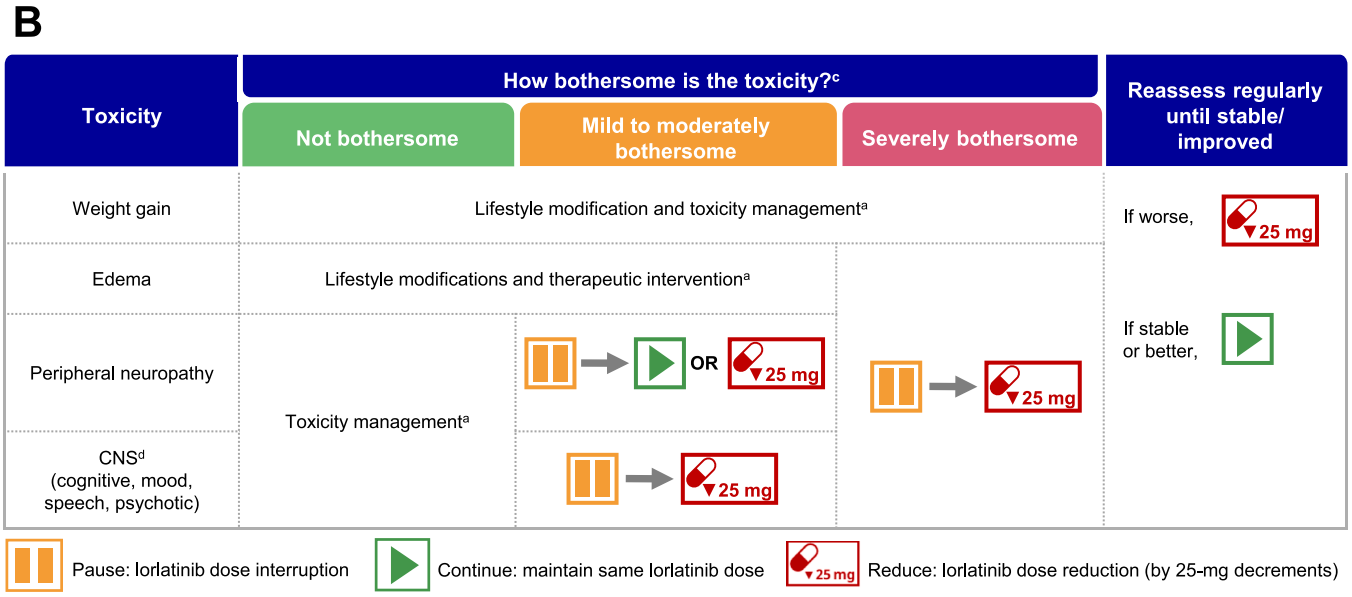


Fig. 3. Management of lorlatinib-induced hyperlipidemia and non-laboratory adverse events. (A) Management of lorlatinib-induced hyperlipidemia. (B) Management of non-laboratory adverse events, including weight gain, edema, peripheral neuropathy, and CNS effects. AE, adverse event; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; ULN, upper limit of normal. [a]Mitigation strategies are provided in Table 2. [b]Cholesterol and triglyceride threshold values can be modified based on overall cardiovascular risk and life expectancy. [c]As severity increases, add management from left to right. For example, for edema that is severely bothersome, consider lifestyle modifications, therapeutic intervention, dose interruption, and dose reduction. Note that all AEs are subjective; if a patient experiences a moderately bothersome AE that is functionally debilitating or functionally detrimental, this may be interpreted as being severely bothersome after discussion with patient and healthcare provider. This is particularly true for CNS toxicities, for which severely bothersome may equate to any CNS functional detriment. [d]CNS toxicities tend to be bothersome and less likely to respond to mitigation strategies; therefore, early dose reduction in combination with temporary dose interruption may be preferred, and dose escalation after the resolution of symptoms is not recommended.

matched overall cardiovascular risk should be assessed to estimate the total risk burden [30]. If baseline blood lipid levels are elevated and overall cardiovascular risk is high, treatment with a lipid-lowering agent (Table 2) should begin before or concurrently with lorlatinib initiation. If overall risk is low despite abnormal cholesterol levels, a watch-and-wait strategy with frequent monitoring may be used.

All patients should be monitored for elevated blood lipids 1 month after beginning lorlatinib. Patients with normal blood lipid values at monitoring should continue taking lorlatinib and have their blood lipid levels evaluated [18,30] at each follow-up visit. Because lipid metabolism can be disrupted by lorlatinib, in rare instances, it is possible for lipid levels to rise to very high levels by the time of the first follow-up visit; however, in most instances, checking lipids at baseline and at each follow-up visit is sufficient for monitoring.

Management with statins (list of preferred statins is presented in Table 2) is recommended at the first sign of laboratory-evident hyperlipidemia. For hyperlipidemia that persists despite treatment, the recommendation is to increase the dosage or switch to a new lipid-lowering therapy. If maximum statin doses are not lowering levels adequately in patients with hypercholesterolemia, ezetimibe can be added. Fenofibrate can be added to help lower triglyceride levels if statins are insufficient at controlling the triglyceride levels [18,30]. While statins are typically well tolerated, intolerance may occur in the form of undesirable side effects, like myalgia [33,34]. If a patient is statin intolerant or there is a lack of response to maximum lipid-lowering therapies, the patient should be referred to cardiovascular or lipid clinics. Here, specialists may prescribe PCSK9 inhibitors or other alternative lipid-lowering therapies. PCSK9 inhibitors, including alirocumab and evolocumab, lower low-density lipoprotein levels in the blood and are approved in the US and Europe for patients who are statin intolerant [33,34]. In two case studies, PCSK9 inhibitors lowered the serum total cholesterol in patients with hypercholesterolemia caused by lorlatinib [35]. In the rare instances [12] of lipids becoming severely elevated (life-threatening per CTCAE criteria; total cholesterol >500 mg/dL [12.93 mmol/L] or triglycerides >1000 mg/dL [11.29 mmol/L]), lipid levels can be reduced by temporally interrupting lorlatinib and initiating mitigation strategies. Once cholesterol falls to a lower value, such as <400 mg/dL (10.34 mmol/L) and/or triglycerides are <500 mg/dL (5.65 mmol/L), lorlatinib can be reintroduced at the same dose [18,30].

Triglyceride levels >1000 mg/dL (11.29 mmol/L) have been associated with acute pancreatitis, but the threshold varies by individual and has been indicated to be as low as >500 mg/dL (5.65 mmol/L) [30,36,37]. Healthcare providers should be wary of the signs and symptoms. Acute pancreatitis is diagnosed when 2 of 3 characteristics are present: abdominal pain, increased pancreatic enzymes >3 times the upper limit of normal, and imaging evidence of acute pancreatitis [36,37]. Management is based on the severity of acute pancreatitis, but initial treatment may range from conservative treatment with intravenous fluids, bowel rest, and pain control to admission to the intensive care unit. Long-term treatment focuses on lowering triglyceride levels.

While patients are taking lipid-lowering medications, blood lipids should be reassessed monthly until lipid laboratory values have stabilized or improved [30]. If hyperlipidemia remains uncontrolled despite maximal treatment with lipid-lowering agents, only then should dose reductions of lorlatinib be considered [18,30].

4.2. Edema

Edema was reported in 56% of lorlatinib patients in the CROWN study (Table 1) [12]. Lorlatinib-associated edema is most frequently reported as peripheral edema or swelling [18], although facial and periorbital edema have also been reported. Edema occurs with a median time to onset of 42 days and a median duration of 163 days (Fig. 2) [18]. Most patients experience either grade 1 (mild) or 2 (moderate) events; only 4% of patients had a grade 3 (severe) event, however, edema was the most common reason for dose reduction (7%) [12,38]. In practice, determining how much the edema affects the patient or the daily functioning of the patient is a more useful approach than following CTCAE grades of severity.

Edema management strategies are presented in Fig. 3B. Patients should be assessed for illnesses or comorbidities that may cause edema, such as underlying heart disease or renal/thyroid dysfunction [30], and evaluated for signs of edema at each follow-up visit.

If edema is present but is not bothersome, lifestyle modifications (Table 2) should be suggested, with no need to alter the regular follow-up schedule. For edema that is mildly or moderately bothersome, therapeutic interventions such as physiotherapy, lymphatic drainage massage, and compression stockings can provide relief. While there is limited scientific evidence to support the use of diuretics, based on the authors' clinical experience in managing edemas, diuretics can be used as an option for management. However, diuretics may result in electrolyte imbalances, which may increase the risk of prolonged QT intervals and should be used carefully [39,40]. While not reported in CROWN, QT prolongation occurred in 6.4% of the 295 patients who received lorlatinib 100 mg once daily in the phase 1/2 study [18]. Consider regular electrolyte monitoring and potential supplementation to maintain electrolytes within normal range [39,40]. If the edema is persistent, other causes should be considered and healthcare providers are encouraged to consult with the respective specialist (ie, cardiologist, endocrinologist, etc.) to help identify other solutions (Table 2). Severely bothersome edema that greatly impacts patients' day-to-day activities should be managed by maximizing mitigation strategies and temporarily interrupting lorlatinib until symptoms improve, at which point the patient can be rechallenged with lorlatinib at a reduced dose.

Patients with symptoms of bothersome edema should be reassessed approximately monthly and mitigation strategies modulated based on symptom severity. In patients with severely bothersome edema that has not improved upon reassessment, the lorlatinib dose should be further reduced in 25-mg decrements. If symptoms of severe edema improve, lorlatinib therapy can be maintained or, based on clinical judgement, possibly increased if the dose is ≤75 mg, with routine monitoring.

4.3. Weight gain

In the CROWN trial, weight gain was experienced by 44% of patients, and 20% of patients experienced grade 3 weight gain, defined as a ≥20% increase from baseline, during treatment with lorlatinib (Table 1) [12,38]. Weight gain alone rarely led to dose modifications (1% of patients) and no discontinuations due to weight gain were reported. The incidence and prevalence of weight gain tend to increase over time, with a median time to onset of 112 days and median duration of 778 days [12]. Weight gain is not isolated to treatment with lorlatinib but has also been observed in patients treated with other TKIs, most notably alectinib [41]. It is unclear why weight gain is a side effect of treatment with ALK TKIs; however, an increase in appetite has been reported by some patients, suggesting that body weight increase may be associated with increased caloric intake [18].

Weight gain management strategies are described in Fig. 3B. Patients should be advised that they may experience weight gain [18] and should report any impact on QOL. Weight gain is also context dependent as some patients may have incurred unintentional weight loss due to the underlying disease. Thus, it may be preferable to choose a baseline that is the patient's healthy weight prior to cancer diagnosis, rather than their nadir weight. In general, weight gain of 10% above baseline may not warrant intervention, whereas management may be needed for increases of ≥20% [18,32,38]. For weight gain that is not bothersome to the patient, no interventions are generally recommended. Information on lifestyle modifications and toxicity management (Table 2) may be useful for weight gain above an ideal weight, regardless of whether it is bothersome or not; however, recommendations should be personalized with ability/interest taken into consideration. There are currently no

data on the use of semaglutide or other incretins in the management of lorlatinib-induced weight gain. Further studies of the use of incretins to manage lorlatinib-induced weight gain are warranted before any recommendations can be rendered. Any use of semaglutide or other incretins should be per approved indications and under expert physician management of the potential side effects, such as delayed gastric emptying [42,43].

Body weight increases and edema are sometimes experienced concurrently [18]. If weight gain and edema are experienced together, edema should be managed first, as a reduction in edema can influence body weight. Dose modifications for weight gain alone are only recommended if weight continues to be severely bothersome after the addition of lifestyle modifications.

4.4. Peripheral neuropathy

In the CROWN trial, 40% of patients experienced peripheral neuropathy (Table 1), with a median time to symptom onset of 105 days and median duration of 380 days. Dose reductions and discontinuations due to peripheral neuropathy were reported in 3% and 1% of patients, respectively [12]. Lorlatinib-associated peripheral neuropathy is typically mild and reversible following lorlatinib dose modifications. Peripheral neuropathy is primarily experienced as paresthesia, although patients may also experience peripheral sensory neuropathy and muscular weakness. Symptoms are commonly described as tingling, numbness, and pain at night, starting typically in the digits of the hands and feet and then moving more proximally in the extremities. Lorlatinib may exacerbate symptoms in patients with preexisting carpal tunnel syndrome. Patients with peripheral neuropathy often also report weight gain and/or edema [18].

Peripheral neuropathy management strategies are described in Fig. 3B. Prior to initiating therapy, patients should be assessed for any underlying causes of peripheral neuropathy (eg, diabetes) [30] and informed that although peripheral neuropathy is relatively common with lorlatinib therapy, symptoms are usually mild and reversible with dose modifications. At each follow-up visit, patients should be reevaluated for signs and symptoms of peripheral neuropathy. A description of the most common symptoms of peripheral neuropathy (numbness or tingling in the fingers) and examples of functional detriment (ie, difficulty buttoning shirts or jackets) may be useful for patients to aid in monitoring [32].

For peripheral neuropathy that is present but not bothersome, mitigation strategies with lifestyle and/or pharmacological interventions should be applied (Table 2). For mild to moderately bothersome neuropathy, lorlatinib should be temporarily withheld while using toxicity management. Once symptoms resolve, lorlatinib may be reintroduced at the same or reduced dose based on the physician's discretion. In patients with severely bothersome or recurrent peripheral neuropathy, treatment with lorlatinib should be temporarily interrupted while maximizing mitigation strategies until symptoms improve, at which point the patient should be rechallenged at a lower dose.

4.5. CNS effects

In the CROWN study, 39% of patients experienced CNS AEs while taking lorlatinib; however, the majority (86% [50/58] of patients who experienced CNS AEs) were of grade 1/2 severity. In real-world studies of second-line or later lorlatinib treatment, the incidence of CNS AEs varied from 3% to 32%; the discrepancy and low incidence may be a result of mild symptoms not being reported in real-world studies [24,44]. In CROWN, the most common CNS AEs of any grade were cognitive, mood, speech, and psychotic effects (Table 1) [12]. The median times to onset of CNS AEs were 37 days for mood, 44 days for psychotic, 105 days for speech, and 155 days for cognitive effects. Median duration also varied—63 days for psychotic, 192 days for mood, 221 days for cognitive, and 229 days for speech effects (Fig. 2) [12,27]. Most CNS effects (56%) were resolved with either no intervention, concomitant medication, dose modification, or a combination [12]. A key feature is the importance of rapid diagnosis of CNS AEs, as early temporary treatment discontinuation can lead to rapid reversal of such AEs, especially in combination with a dose reduction at the time of reinitiation of lorlatinib therapy.

Cognitive changes are commonly experienced as memory impairment, cognitive disorder, and amnesia. Patients have reported "sluggish thought," "fogginess," "trouble connecting the dots," difficulty multitasking, difficulty finding the right words, issues with short-term memory or recall, and confusion and hallucinations in severe cases [18]. Within the trials, cognitive AEs led to dose reduction and permanent discontinuation in 2% and 1% of patients, respectively [12]. Pragmatically, early reduction may lead to improved AE symptoms faster. Mood changes associated with lorlatinib are most often reported as irritability, anxiety, depression, and affect lability. When patients first start treatment with lorlatinib, some report feeling a little "energized" or "buzzed." Patients also report "feeling flat" and/or "feeling less excited about things" [18]. Dose reductions due to mood effects were reported in 2% of patients in the clinical trials [12]; early identification of this AE and dose modification may aid in restoration of function and QOL faster. Psychotic effects (typically hallucinations) were reported in 5% of patients in the CROWN study, and dose reductions due to psychotic effects occurred in 1% of patients [12,27]. Speech effects included dysarthria, slow speech, and speech disorder [18]. Dose reductions due to speech effects were experienced by 1% of patients [12]. In the CROWN study, no patient permanently discontinued treatment based on mood, psychotic, or speech effects [12]. It is important to note that the majority of CNS AEs do not present as psychosis but are actually more similar to how patients describe their cognitive abilities while receiving chemotherapy, often referred to as "chemo fog."

Management strategies for CNS effects are described in Fig. 3B. Because of the near-complete control of CNS disease from lorlatinib, it is reasonable to interrupt lorlatinib administration temporarily at the first instance of presumed CNS AEs and wait up to a week or two for improvement, before seeking brain imaging; this is because the vast majority of lorlatinib-associated CNS AEs will abate within a few days of temporary dose interruption. Brain imaging can be considered in the presence of residual or severe CNS symptoms. Some patients, particularly those with brain metastases, brain radiation, psychiatric illness, and use of neurotropic medication, may be predisposed to developing CNS AEs while taking lorlatinib [19]. Patients with these risk factors should be more closely monitored for the development of CNS AEs and may be considered for a lower starting dose of lorlatinib. Caregivers, family members, and patients should be encouraged to report any changes in cognitive ability, mood (including irritability), or speech patterns during treatment with lorlatinib and assured that these changes (including apparent personality changes) can be generally managed with dose modifications and are usually temporary [18,30]. At every visit, asking questions regarding memory problems, impaired judgment, changes in mood or interactions with family members, and a quick review of the CNS AEs can help trigger early reporting.

Patients should be referred to specialists (ie, psychiatrists, neurologists) only when temporary dose interruption and dose reduction do not result in elimination or improvement in CNS symptoms, to ensure the cause of the CNS symptoms is not a psychiatric or neurologic disorder. Unlike other AEs, for symptoms of CNS AEs that are even mildly to moderately bothersome, lorlatinib should be temporally withheld until symptoms improve and subsequently reintroduced; this may be the rare instance in which early dose reduction should be implemented, even with mild symptoms. Certainly, for the rare patient with severe CNS AE symptoms, temporary dose interruption and dose reduction are mandatory. Absence of significant improvement within a few weeks of dose interruption may trigger further psychiatric or neurologic evaluation, with the help of specialists, as lorlatinib may rarely trigger or worsen pre-existing psychiatric or neurologic disorders. Close follow-up

during dose interruption (even sometimes weekly in extreme cases) and regular follow-up after dose reduction are encouraged. Most cases can be managed using this approach, with good results and maintenance of long-term use of lorlatinib.

5. Challenges and limitations of "prepare, monitor, manage, reassess" for AE management

This guide is focused on the most common AEs (hyperlipidemia, edema, weight gain, peripheral neuropathy, and CNS effects) attributed to the unique safety profile of lorlatinib (Table 1) [12,18]. While the guide provides detailed management strategies for those AEs, it does not address management strategies for other common AEs experienced with lorlatinib, such as gastrointestinal effects and fatigue [13]. However, these AEs are also common with the other ALK TKIs and other cancer treatments; therefore, prior publications addressing management strategies for these common AEs are also applicable to lorlatinib [20,21,28,45,46].

Another potential challenge with the framework of this AE management approach is the frequency of monitoring and reassessing appointments. Since the median PFS with first-line lorlatinib has not been reached after 36.7 months of follow-up in CROWN [12], patients are expected to be on treatment for years. Therefore, while this AE management framework may be proactive, adherence to the schedule may decline after years of treatment. Initially, the patient should be assessed frequently after beginning lorlatinib treatment, but the long-term frequency of follow-up appointments may vary based on healthcare provider discretion.

6. Conclusions

Lorlatinib is an effective treatment option for patients with ALK-positive metastatic NSCLC.[6] Lorlatinib has a distinct safety profile [18,19]. With appropriate and immediate therapy management, patient tolerability can be preserved in conjunction with clinical benefit [12,26,27]. Proactive therapy management requires general knowledge regarding the symptoms, incidence, and timeline of common lorlatinib-associated AEs, as well as open communication between healthcare providers, patients, and caregivers. The healthcare team can educate patients and their caregivers on the timeline and incidence rates of lorlatinib AEs. The schema of "prepare, monitor, manage, reassess" outlined here provides a patient-centric and pragmatic framework for lorlatinib AE management that can be easily implemented in routine clinical practice with the goal of maintaining patient QOL and disease control. A focus on both subjective (how bothersome is the AE) and objective (how functionally detrimental is the AE) aspects of the AE provides a pragmatic basis for management. Once AEs are recognized, management strategies include mitigation strategies (such as lifestyle modifications and addition of symptom-relief concomitant medications) and/or dose modifications based on the impact of non-laboratory AEs on patient lifestyle and QOL. The decision to use mitigation strategies should be reassessed frequently, and lorlatinib doses may be titrated up or down as symptoms change without sacrificing efficacy. A video summary of this manuscript is available as part of the Supplement.

CRediT authorship contribution statement

Geoffrey Liu: Writing – review & editing. **Julien Mazieres:** Writing – review & editing. **Jan Stratmann:** Writing – review & editing. **Sai-Hong Ignatius Ou:** Writing – review & editing. **Tony Mok:** Writing – review & editing. **Mary Grizzard:** Writing – review & editing. **Yasushi Goto:** Writing – review & editing. **Enriqueta Felip:** Writing – review & editing. **Benjamin J. Solomon:** Writing – review & editing. **Todd M. Bauer:** Writing – review & editing.

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Appendix A. Supplementary data

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References

[1] American Cancer Society, Lung cancer early detection, diagnosis, and staging. https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging.html (accessed 20 July 2023).
[2] M. Chevallier, M. Borgeaud, A. Addeo, A. Friedlaender, Oncogenic driver mutations in non-small cell lung cancer: past, present and future, World J. Clin. Oncol. 12 (4) (2021) 217–237, https://doi.org/10.5306/wjco.v12.i4.217.
[3] K.C. Arbour, G.J. Riely, Diagnosis and treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer, Hematol. Oncol. Clin. North Am. 31 (1) (2017) 101–111, https://doi.org/10.1016/j.hoc.2016.08.012.
[4] W.Q. Wang, T. Xu, J.J. Zhang, Y. Wang, Y. Wang, W. Zhang, J.G. Zhu, A comprehensive clinical evaluation of first-line drugs for ALK-positive advanced non-small cell lung cancer, J. Thorac. Dis. 15 (4) (2023) 1935–1947, https://doi.org/10.21037/jtd-23-380.
[5] L.E. Hendriks, K.M. Kerr, J. Menis, T.S. Mok, U. Nestle, A. Passaro, S. Peters, D. Planchard, E.F. Smit, B.J. Solomon, G. Veronesi, M. Reck, Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, Ann. Oncol. 34 (4) (2023) 339–357, https://doi.org/10.1016/j.annonc.2022.12.013.
[6] L. Wang, W. Wang, Safety and efficacy of anaplastic lymphoma kinase tyrosine kinase inhibitors in non-small cell lung cancer, Oncol. Rep. 45 (1) (2021) 13–28, https://doi.org/10.3892/or.2020.7851.
[7] H.Y. Zou, L. Friboulet, D.P. Kodack, L.D. Engstrom, Q. Li, M. West, R.W. Tang, H. Wang, K. Tsaparikos, J. Wang, S. Timofeevski, R. Katayama, D.M. Dinh, H. Lam, J.L. Lam, S. Yamazaki, W. Hu, B. Patel, D. Bezwada, R.L. Frias, E. Lifshits, S. Mahmood, J.F. Gainor, T. Affolter, P.B. Lappin, H. Gukasyan, N. Lee, S. Deng, R. K. Jain, T.W. Johnson, A.T. Shaw, V.R. Fantin, T. Smeal, PF-06463922, an ALK/ROS1 inhibitor, overcomes resistance to first and second generation ALK inhibitors in preclinical models, Cancer Cell 28 (1) (2015) 70–81, https://doi.org/10.1016/j.ccell.2015.05.010.
[8] T.W. Johnson, P.F. Richardson, S. Bailey, A. Brooun, B.J. Burke, M.R. Collins, J. J. Cui, J.G. Deal, Y.L. Deng, D. Dinh, L.D. Engstrom, M. He, J. Hoffman, R. L. Hoffman, Q. Huang, R.S. Kania, J.C. Kath, H. Lam, J.L. Lam, P.T. Le, L. Lingardo, W. Liu, M. McTigue, C.L. Palmer, N.W. Sach, T. Smeal, G.L. Smith, A.E. Stewart, S. Timofeevski, H. Zhu, J. Zhu, H.Y. Zou, M.P. Edwards, Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations, J. Med. Chem. 57 (11) (2014) 4720–4744, https://doi.org/10.1021/jm500261q.
[9] A.T. Shaw, E. Felip, T.M. Bauer, B. Besse, A. Navarro, S. Postel-Vinay, J.F. Gainor, M. Johnson, J. Dietrich, L.P. James, J.S. Clancy, J. Chen, J.F. Martini, A. Abbattista, B.J. Solomon, Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial, Lancet Oncol. 18 (12) (2017) 1590–1599, https://doi.org/10.1016/S1470-2045(17)30680-0.
[10] B.J. Solomon, B. Besse, T.M. Bauer, E. Felip, R.A. Soo, D.R. Camidge, R. Chiari, A. Bearz, C.C. Lin, S.M. Gadgeel, G.J. Riely, E.H. Tan, T. Seto, L.P. James, J. S. Clancy, A. Abbattista, J.F. Martini, J. Chen, G. Peltz, H. Thurm, S.I. Ou, A. T. Shaw, Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study, Lancet Oncol. 19 (12) (2018) 1654–1667, https://doi.org/10.1016/S1470-2045(18)30649-1.
[11] A.T. Shaw, T.M. Bauer, F. de Marinis, E. Felip, Y. Goto, G. Liu, J. Mazieres, D. W. Kim, T. Mok, A. Polli, H. Thurm, A.M. Calella, G. Peltz, B.J. Solomon, First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer, N. Engl. J. Med. 383 (21) (2020) 2018–2029, https://doi.org/10.1056/NEJMoa2027187.
[12] B.J. Solomon, T.M. Bauer, T.S.K. Mok, G. Liu, J. Mazieres, F. de Marinis, Y. Goto, D. W. Kim, Y.L. Wu, J. Jassem, F.L. López, R.A. Soo, A.T. Shaw, A. Polli, R. Messina, L. Iadeluca, F. Toffalorio, E. Felip, Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study, Lancet Respir. Med. 11 (4) (2023) 354–366, https://doi.org/10.1016/S2213-2600(22)00437-4.
[13] Pfizer, Lorbrena (lorlatinib) prescribing information. https://labeling.pfizer.com/ShowLabeling.aspx?id=11140 (accessed 20 July 2023).
[14] European Medicines Agency, Lorviqua summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/lorviqua-epar-product-information_en.pdf (accessed 20 July 2023).
[15] Health Canada, Lorbrena product monograph including patient medication information. https://pdf.hres.ca/dpd_pm/00061480.PDF (accessed 20 July 2023).
[16] Australian Therapeutic Goods Administration, Lorviqua. https://www.tga.gov.au/resources/auspmd/lorviqua (accessed 20 July 2023).
[17] T. Seto, H. Hayashi, M. Satouchi, Y. Goto, S. Niho, N. Nogami, T. Hida, T. Takahashi, J. Sakakibara-Konishi, M. Morise, T. Nagasawa, M. Suzuki, M. Ohkura, K. Fukuhara, H. Thurm, G. Peltz, M. Nishio, Lorlatinib in previously treated anaplastic lymphoma kinase-rearranged non-small cell lung cancer: Japanese subgroup analysis of a global study, Cancer Sci. 111 (10) (2020) 3726–3738, https://doi.org/10.1111/cas.14576.
[18] T.M. Bauer, E. Felip, B.J. Solomon, H. Thurm, G. Peltz, M.D. Chioda, A.T. Shaw, Clinical management of adverse events associated with lorlatinib, Oncologist 24 (8) (2019) 1103–1110, https://doi.org/10.1634/theoncologist.2018-0380.
[19] I. Dagogo-Jack, A. Abbattista, J.F. Murphy, S. Krulewicz, A. Do, J. Peterson, J. J. Lin, J.F. Gainor, R. Messina, E.A. Krueger, H. Thurm, B.Y. Yeap, Factors associated with developing neurocognitive adverse events in patients receiving lorlatinib after progression on other targeted therapies, J. Thorac. Oncol. 18 (1) (2023) 67–78, https://doi.org/10.1016/j.jtho.2022.09.219.
[20] T. Mok, D.R. Camidge, S.M. Gadgeel, R. Rosell, R. Dziadziuszko, D.W. Kim, M. Pérol, S.I. Ou, J.S. Ahn, A.T. Shaw, W. Bordogna, V. Smoljanović, M. Hilton, T. Ruf, J. Noé, S. Peters, Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study, Ann. Oncol. 31 (8) (2020) 1056–1064, https://doi.org/10.1016/j.annonc.2020.04.478.
[21] D.R. Camidge, H.R. Kim, M.J. Ahn, J.C.H. Yang, J.Y. Han, M.J. Hochmair, K.H. Lee, A. Delmonte, M.R. Garcia Campelo, D.W. Kim, F. Griesinger, E. Felip, R. Califano, A.I. Spira, S.N. Gettinger, M. Tiseo, H.M. Lin, Y. Liu, F. Vranceanu, H. Niu, P. Zhang, S. Popat, Brigatinib versus crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: final results of phase 3 ALTA-1L trial, J. Thorac. Oncol. 16 (12) (2021) 2091–2108, https://doi.org/10.1016/j.jtho.2021.07.035.
[22] V.W. Zhu, Y.T. Lin, D.W. Kim, H.H. Loong, M. Nagasaka, H. To, Y.L. Ang, C.Y. Ock, N. Tchekmedyian, S.I. Ou, N.L. Syn, T. Reungwetwattana, C.C. Lin, R.A. Soo, An international real-world analysis of the efficacy and safety of lorlatinib through early or expanded access programs in patients with tyrosine kinase inhibitor-refractory ALK-positive or ROS1-positive NSCLC, J. Thorac. Oncol. 15 (9) (2020) 1484–1496, https://doi.org/10.1016/j.jtho.2020.04.019.
[23] N. Peled, R. Gillis, S. Kilickap, P. Froesch, S. Orlov, E. Filippova, U. Demirci, P. Christopoulos, I. Cicin, F.B. Basal, C. Yilmaz, M. Fedor, T. Korkmaz, S. Paydas, O. Gautschi, A. Zirtiloglu, Y. Eralp, H.Y. Cinkir, A. Sezer, M. Erman, D. Tural, H. Turna, J. Mazieres, E. Dudnik, N. Reguart, D.R. Camidge, T.L. Ng, F.C. Senler, I. Beypinar, D. Yazilitas, A. Demirkazik, A. Karaoglu, K. Okutur, H.S. Coskun, M.A. N. Sendur, A. Isikdogan, D. Cabuk, P.F. Yumuk, I. Yildiz, M.A. Kaplan, O. Ozyilkan, I. Oztop, O.F. Olmez, K. Aydin, A. Aydiner, N. Meydan, R.D. Grinberg, L. C. Roisman, GLASS: global lorlatinib for ALK(+) and ROS1(+) retrospective study:

real world data of 123 NSCLC patients, Lung Cancer 148 (2020) 48–54, https://doi.org/10.1016/j.lungcan.2020.07.022.
[24] J.Y. Shih, Y.H. Luo, G.C. Chang, J.W. Chang, C.C. Wang, T.Y. Yang, W.T. Fang, W. Y. Shau, Real-world evidence of lorlatinib therapy in Taiwanese patients with advanced anaplastic lymphoma kinase-positive non-small cell lung cancer, J. Formos. Med. Assoc. (2024), https://doi.org/10.1016/j.jfma.2023.12.019.
[25] P.H. Lee, K.C. Chen, K.H. Hsu, Y.H. Huang, J.S. Tseng, T.Y. Yang, G.C. Chang, Real-world efficacy and safety of lorlatinib in treating advanced ALK-positive non-small cell lung cancer patients, Anticancer Drugs 32 (10) (2021) 1099–1104, https://doi.org/10.1097/CAD.0000000000001107.
[26] J. Mazieres, L. Iadeluca, A.T. Shaw, B.J. Solomon, T.M. Bauer, F. de Marinis, E. Felip, Y. Goto, D.W. Kim, T. Mok, A. Reisman, H. Thurm, A.M. Polli, G. Liu, Patient-reported outcomes from the randomized phase 3 CROWN study of first-line lorlatinib versus crizotinib in advanced ALK-positive non-small cell lung cancer, Lung Cancer 174 (2022) 146–156, https://doi.org/10.1016/j.lungcan.2022.11.004.
[27] B.J. Solomon, T.M. Bauer, S.H. Ignatius Ou, G. Liu, H. Hayashi, A. Bearz, K. Penkov, Y.L. Wu, O. Arrieta, J. Jassem, A.M. Calella, G. Peltz, A. Polli, H. Thurm, T. Mok, Post hoc analysis of lorlatinib intracranial efficacy and safety in patients with ALK-positive advanced non-small-cell lung cancer from the phase III CROWN study, J. Clin. Oncol. 40 (31) (2022) 3593–3602, https://doi.org/10.1200/JCO.21.02278.
[28] F. Zhou, Y. Yang, L. Zhang, Y. Cheng, B. Han, Y. Lu, C. Wang, Z. Wang, N. Yang, Y. Fan, L. Wang, Z. Ma, L. Zhang, Y. Yao, J. Zhao, X. Dong, B. Zhu, C. Zhou, Expert consensus of management of adverse drug reactions with anaplastic lymphoma kinase tyrosine kinase inhibitors, ESMO Open 8 (3) (2023) 101560, https://doi.org/10.1016/j.esmoop.2023.101560.
[29] A. Bearz, E. Felip, J. Mazieres, F. de Marinis, T. Bauer, A. Polli, R. Messina, H. Thurm, D. Thomaidou, T.S.K. Mok, B.J. Solomon, 979P Long-term intracranial safety and efficacy analyses from the phase III CROWN study, Ann. Oncol. 33 S998-S999, https://doi.org/10.1016/j.annonc.2022.07.1107.
[30] F. Barata, C. Aguiar, T.R. Marques, J.B. Marques, V. Hespanhol, Monitoring and managing lorlatinib adverse events in the Portuguese clinical setting: a position paper, Drug Saf. 44 (8) (2021) 825–834, https://doi.org/10.1007/s40264-021-01083-x.
[31] J. Chen, H. Xu, S. Pawlak, L.P. James, G. Peltz, K. Lee, K. Ginman, M. Bergeron, Y. K. Pithavala, The effect of rifampin on the pharmacokinetics and safety of lorlatinib: results of a phase one, open-label, crossover study in healthy participants, Adv. Ther. 37 (2) (2020) 745–758, https://doi.org/10.1007/s12325-019-01198-9.
[32] M. Reed, A.S. Rosales, M.D. Chioda, L. Parker, G. Devgan, J. Kettle, Consensus recommendations for management and counseling of adverse events associated with lorlatinib: a guide for healthcare practitioners, Adv. Ther. 37 (6) (2020) 3019–3030, https://doi.org/10.1007/s12325-020-01365-3.
[33] R. Alonso, A. Cuevas, A. Cafferata, Diagnosis and management of statin intolerance, J. Atheroscler. Thromb. 26 (3) (2019) 207–215, https://doi.org/10.5551/jat.RV17030.
[34] M.P. Manniello, Alirocumab (Praluent): first in the new class of PCSK9 inhibitors, Pharm. Therap. 41 (1) (2016) 28–53.
[35] N.I. Khairunnisa, F. Yamasaki, Y.O. Miyati, M.N. Horie, The efficacy of PCSK9 inhibitors in treating hypercholesterolemia caused by lorlatinib: a report of two cases, Clin. Lung Cancer 24 (5) (2023) EE176-E178, https://doi.org/10.1016/j.cllc.2023.03.016.
[36] R. Garg, T. Rustagi, Management of hypertriglyceridemia induced acute pancreatitis, Biomed. Res. Int. 2018 (2018) 4721357, https://doi.org/10.1155/2018/4721357.
[37] N. de Pretis, A. Amodio, L. Frulloni, Hypertriglyceridemic pancreatitis: epidemiology, pathophysiology and clinical management, United European Gastroenterol. J. 6 (5) (2018) 649–655, https://doi.org/10.1177/2050640618755002.
[38] US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accessed 21 February 2023).
[39] S. Aramapatzis, G.C. Funk, A.B. Liechtle, G.M. Fiedler, C. Schwarz, H. Zimmermann, A.K. Exadaktylos, G. Lidner, Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis, BMC Med. 11 (2013) 83, https://doi.org/10.1186/1741-7015-11-83.
[40] R. Khatib, F.R.N. Sabir, C. Omari, C. Pepper, M.H. Tayebjee, Managing drug-induced QT prolongation in clinical practice, Postgrad Med. J. 97 (1149) (2021) 452–458, https://doi.org/10.1136/postgradmedj-2020-138661.
[41] S.P. de Leeuw, M.A. Pruis, B.J. Sikkema, M. Mohseni, G.D.M. Veerman, M.S. Paats, D.W. Dumoulin, E.F. Smit, A. Schols, R.H.J. Mathijssen, E.F.C. van Rossum, A. C. Dingemans, Analysis of serious weight gain in patients using alectinib for ALK-positive lung cancer, J. Thorac. Oncol. 18 (8) (2023) 1017–1030, https://doi.org/10.1016/j.jtho.2023.03.020.
[42] K. Dahl, A. Brooks, F. Almazedi, S.T. Hoff, C. Boschini, T.A. Baekdal, Oral semaglutide improves postprandial glucose and lipid metabolism, and delays gastric emptying, in subjects with type 2 diabetes, Diabetes Obes. Metab. 23 (7) (2021) 1594–1603, https://doi.org/10.1111/dom.14373.
[43] M. Camilleri, Gastrointestinal hormones and regulation of gastric emptying, Curr. Opin. Endocrinol. Diabetes Obes. 26 (1) (2019) 3–10, https://doi.org/10.1097/med.0000000000000448.
[44] J. Schoenmaekers, J. Dijkstra, A. van der Wekken, M. Paats, M. Broen, L. Brandts, A.M. Dingemans, L. Hendriks, In-depth analysis of lorlatinib-related neurocognitive adverse events in patients with non-small-cell lung cancer, Clin Lung Cancer (23) (2023), https://doi.org/10.1016/j.cllc.2023.12.003.
[45] M.J. Berger, D.S. Ettinger, J. Aston, S. Barbour, J. Bergsbaken, P.J. Bierman, D. Brandt, D.E. Dolan, G. Ellis, E.J. Kim, S. Kirkegaard, D.D. Kloth, R. Lagman, D. Lim, C. Loprinzi, C.X. Ma, V. Maurer, L.B. Michaud, L.M. Nabell, K. Noonan, E. Roeland, H.S. Rugo, L.S. Schwartzberg, B. Scullion, J. Timoney, B. Todaro, S. G. Urba, D.A. Shead, M. Hughes, NCCN guidelines insights: antiemesis, version 2.2017, J. Natl. Compr. Canc. Netw. 15 (7) (2017) 883–893, https://doi.org/10.6004/jnccn.2017.0117.
[46] A.M. Berger, K. Mooney, A. Alvarez-Perez, W.S. Breitbart, K.M. Carpenter, D. Cella, C. Cleeland, E. Dotan, M.A. Eisenberger, C.P. Escalante, P.B. Jacobsen, C. Jankowski, T. LeBlanc, J.A. Ligiberl, E.T. Loggers, B. Mandrell, B.A. Murphy, O. Palesh, W.F. Pirl, S.C. Plaxe, M.B. Riba, H.S. Rugo, C. Salvador, L.I. Wagner, N. D. Wagner-Johnston, F.J. Zachariah, M.A. Bergman, C. Smith, Cancer-related fatigue, version 2.2015: clinical practice guidelines in oncology, J. Natl. Compr. Canc. Netw. 13 (8) (2015) 1012–1039, https://doi.org/10.6004/jnccn.2015.0122.
[47] N. Blais, J.P. Adam, J. Nguyen, J.C. Grégoire, Evaluation and management of dyslipidemia in patients treated with lorlatinib, Curr. Oncol. 28 (1) (2021) 265–272, https://doi.org/10.3390/curroncol28010029.