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REVIEW

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Lorlatinib atypical safety profile in ALK-positive aNSCLC: tips for management from an Italian expert panel

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ABSTRACT

Lorlatinib is a third-generation tyrosine kinase inhibitor approved for first- and second-line treatment of ALK-positive advanced non-small cell lung cancer. The CROWN study demonstrated that first-line lorlatinib significantly improves progression-free survival and intracranial control compared to crizotinib, with sustained benefits observed over a follow-up period of up to 5 years. As lorlatinib is associated with a distinct adverse event (AE) profile, we aim to analyze lorlatinib's safety profile, focusing on AEs incidence, severity, timing and management. A comprehensive safety management framework is also outlined to address lorlatinib-associated toxicity, drawing on evidence from the literature and the clinical expertise of an Italian expert panel. The most frequent AEs associated with lorlatinib are hypercholesterolemia and hypertriglyceridemia, which emerge early after treatment initiation. The 5-year analysis of the CROWN study revealed minimal changes in most AE rates over time. Pharmacological and non-pharmacological approaches effectively resolved most AEs; lorlatinib dose reduction did not affect its efficacy. The proposed safety management framework emphasizes patient preparation and regular monitoring to predict AE occurrence, indicating AE-specific interventions, mitigation strategies and multidisciplinary collaboration to optimize outcomes. Lorlatinib's toxicity appears generally predictable and manageable; the safety framework offers pragmatic guidance to clinicians for appropriate management in clinical practice.

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Lorlatinib; ALK-positive aNSCLC; safety; adverse events; management

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer types and is associated with a poor prognosis [1]. The understanding of NSCLC oncogenic driver mutations has allowed the development of specific tyrosine kinase inhibitors (TKIs), considerably extending the survival expectation over the last years [2]. Among driver mutations, anaplastic lymphoma kinase (ALK) genomic alterations are found in 3–7% of NSCLC patients [1,3–5]. First- (crizotinib) and second-generation (alectinib, brigatinib, ensartinib, ceritinib) TKIs are effective therapeutic options for the management of patients with ALK+ advanced NSCLC (aNSCLC) [2]; among second-generation TKIs, alectinib and brigatinib show a higher level of evidence for treating patients with CNS involvement than ceritinib [6]. However, newly emerging acquired ALK mutations conferring resistance to second-generation TKI pose a therapeutic challenge, as they limit the available treatment options. Lorlatinib is a potent third-generation TKI that targets both ALK and c-ROS oncogene 1 receptor tyrosine kinase (ROS1). Key differences between lorlatinib and previous ALK TKIs include: i) retained function against acquired ALK mutations associated with second-generation TKI resistance (including G1202R mutation) and ii) higher blood-brain barrier penetration and intracranial activity against brain metastases [7,8].

Pivotal phase I and II clinical trials demonstrated the systemic and intracranial efficacy of lorlatinib in patients with or without previous chemotherapy, mainly pre-treated with first and second-generation TKIs [9,10]. The positive results of these clinical trials granted lorlatinib accelerated approval by the Food and Drug Administration (FDA) in November 2018, for second or third-line treatment in patients with ALK+ advanced metastatic NSCLC [11]. More recently, the CROWN phase III trial's compelling evidence of lorlatinib's superiority over crizotinib and efficacy in TKIs naïve patients fueled its extended approval as first-line treatment [12,13]. In Italy, lorlatinib received full reimbursement approval for first-line treatment in November 2023 [14].

The recently released CROWN updates strengthen the clinically meaningful, sustained and greater efficacy of lorlatinib over crizotinib [15]. After a 5-year follow-up, median PFS was not reached by lorlatinib-treated patients, while it was 9.1 months in the crizotinib group; 5-year PFS were 60% and 8%, respectively. The median time to intracranial progression still favored lorlatinib over crizotinib (not reached vs 16.4 months, respectively). Lorlatinib was associated with a 96% probability of patients remaining free from brain metastases at 5 years [15]. Although a direct comparison between first- and later-line use of lorlatinib has not been conducted, the available data [10,16] suggest an unprecedented superior systemic and intracranial efficacy of first-line lorlatinib in the ALK TKIs landscape [17].

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Article highlights

- Lorlatinib's safety profile is unique. Analyses from clinical trials and real-world studies demonstrate that its associated AEs are both predictable and manageable with appropriate interventions.
- The safety management framework outlined by an Italian expert panel provides clinicians with actionable strategies to address adverse events potentially emerging during lorlatinib treatment.
- By emphasizing open communication, proactive monitoring, tailored interventions, regular follow-ups and multidisciplinary collaboration, the framework supports the safe integration of lorlatinib into first-line therapy for ALK-positive aNSCLC.
- This guidance empowers healthcare providers to personalize care and improve patient outcomes and the overall quality of life for individuals undergoing lorlatinib therapy.

Despite the lack of direct comparison among new agents, indirect evaluations, systematic reviews and network meta-analyses confirmed the highest long-term global and intracranial PFS rates in patients with and without brain metastases receiving lorlatinib [18–24]. Results from matching-adjusted indirect analyses (MAICs) supported the superior efficacy of first-line lorlatinib in extending PFS over alectinib and brigatinib [24], with the 5-year CROWN data further substantiating the long-term PFS benefit of lorlatinib compared to alectinib [25]. Considering the growing body of evidence, lorlatinib is poised to become the new first-line standard treatment in clinical practice.

Lorlatinib treatment carries a unique safety profile with some specific adverse events (AEs) that deserve attention and detailed information from oncologists to patients and caregivers. By providing a comprehensive summary of AEs associated with lorlatinib, this review highlights the overall predictability and manageability of lorlatinib's toxicity, particularly within the first-line setting. The following sections discuss the types, frequency, and severity of AEs documented in both clinical trials and real-world, outlining the recommended strategies for their effective management. Drawing on their experience with lorlatinib in the Italian clinical practice, the authors provide valuable insights into managing patient safety during treatment.

2. Lorlatinib safety profile and management: data from clinical trials

The spectrum of AEs observed in patients treated with lorlatinib is heterogeneous and does not completely overlap with the safety profile of other TKIs. AEs are usually well-tolerated. In the phase I/II study, adverse drug reactions (ADRs) to lorlatinib (i.e., those AEs that are likely caused by lorlatinib treatment) of grade 3 or 4 included hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy [26]. Among these, hypercholesterolemia and hypertriglyceridemia seem to be associated with lorlatinib use [27]. The increased hepatocytes' intracellular lipid levels and renal impairment might contribute to lorlatinib-associated hyperlipidemia, but the exact mechanisms are still uncertain [28]. CNS AEs have been linked to lorlatinib, although also observed in patients treated with other ALK TKIs [29]. While the mechanism underlying psychiatric AEs in ALK inhibitors use is unclear, research suggests that ALK regulates the internalization of the dopamine D2 receptor, a G protein-coupled receptor expressed in brain regions that control motor function, cognition, and motivation [30].

2.1. Data from the CROWN study: first-line lorlatinib

Figure 1 displays the type, frequency and severity of AEs occurring during the CROWN study (N = 149 patients) after 18.3 months (initial analysis, data cutoff: March 2020) [13], 36.7 months (updated analysis) [31] and 60.2 months (latest analysis) [15] of follow-up. All patients experienced at least one AE. In the initial analysis (18.3 months), any grade hypercholesterolemia (70%), hypertriglyceridemia (64%), edema (55%), weight gain (38%) and peripheral neuropathy (34%) were the most frequent AEs. The most frequent CNS AEs of any grade were cognitive and mood effects, in 21% and 16% of patients, respectively [13].

Notably, a *post hoc* analysis of the initial CROWN study data (cutoff: March 2020) reported 86 CNS AEs from 52 patients in the lorlatinib group. Of those AEs, the majority (62%) were managed without intervention. Among these, 53% resolved spontaneously, while 45% remained unresolved but were predominantly of grade 1 severity. Only 2% of the cases led to permanent treatment discontinuation due to grade 2 and grade 3 confusion [32]. Lorlatinib dose modification (reduction and/or interruption, with or without concomitant medication) resolved AEs in 23% of the cases [32]. Cognitive effects were more frequent among patients with brain metastases (42%) than without (32%). Overall, the incidence of CNS AEs was higher in patients previously treated with brain radiotherapy (56% vs 34% in those not subjected to radiotherapy) [32]. The latest CROWN analysis confirmed this finding; however, the number of patients receiving prior brain radiotherapy (n = 9) was much lower than the number of patients without prior radiotherapy (n = 140) [15].

In the initial CROWN analysis, most common grade ≥3 AEs were hypercholesterolemia (16%) and hypertriglyceridemia (24%); other common grades ≥3 AEs were weight gain and hypertension, registered in 17% and 10% of patients, respectively. Grade ≥3 CNS AEs were generally low, with 2% of patients experiencing cognitive effects and 1% experiencing mood, speech and psychotic effects [13].

Compared to the initial CROWN analysis, the updated and latest analyses of the CROWN study revealed either no or minimal changes in AE rates. No new safety signals were identified during the extended follow-up. After 5 years, the majority of non-CNS AEs of any grade – including hypercholesterolemia, hypertriglyceridemia, edema – increased by 2% or less compared to the initial analysis (Figure 1) [15].

The CROWN study showed higher rates of hyperlipidemia (including both hypercholesterolemia and hypertriglyceridemia) upon lorlatinib treatment compared with crizotinib (Table 1) [13,15,31]. Despite this difference, the latest CROWN analysis showed similar rates of any grade cardiovascular AEs between the two arms (28% in both; grade ≥3: 8% for lorlatinib vs. 9% for crizotinib) (Table 1) [15]. Among patients with hyperlipidemia (either at baseline or developed during the study), the rate of any

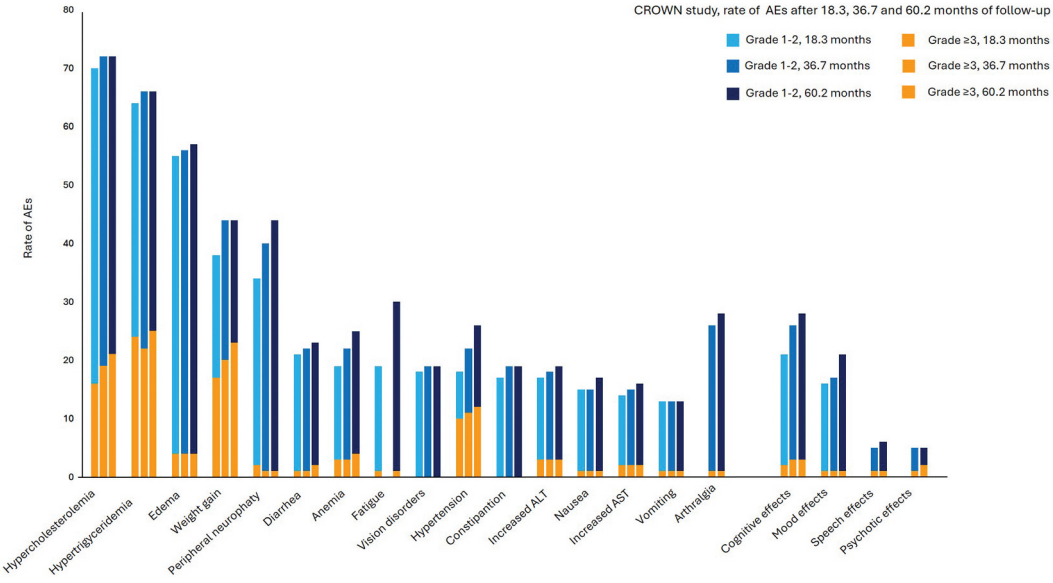

Figure 1. Types and rates of any grade and grade ≥3 AEs occurring in lorlatinib-treated patients in the CROWN study, after 18.3, 36.7 and 60.2 months of follow-up (first, second and third column, respectively, for each AE). The initial analysis shows only AEs differing by >10% between lorlatinib and crizotinib arms [13]. The updated analysis reports non-CNS AEs differing by >10% between lorlatinib and crizotinib arms, and all CNS AEs [31]. The latest analysis shows non-CNS AEs occurring in ≥10% irrespectively of differences between treatment arms, and all CNS AEs [15].

Abbreviations: AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CNS: central nervous system.

Table 1. Rates of any grade and ≥3 grade hypercholesterolemia, hypertriglyceridemia, hyperlipidemia and any cardiovascular AEs in lorlatinib vs crizotinib arms, data from the latest CROWN study [15]. Data are expressed as percentages.

	Lorlatinib (n = 149)	Crizotinib (n = 142)
Hypercholesterolemia, any grade	72	4
Hypercholesterolemia, grade ≥3	21	0
Hypertriglyceridemia, any grade	66	6
Hypertriglyceridemia, grade ≥3	25	0
Any cardiovascular AEs, any grade	28	28
Any cardiovascular AEs, grade ≥3	8	9
	Lorlatinib (patients with hyperlipidemia, n = 134)	**Crizotinib (patients with hyperlipidemia, n = 32)**
Any cardiovascular AEs, any grade	28	47
Any cardiovascular AEs, grade ≥3	7	9

grade cardiovascular AEs was higher in crizotinib group (46%) compared to lorlatinib group (28%), while rates of grade ≥3 AEs were comparable (Table 1) [15]. These findings suggest that lorlatinib-induced hyperlipidemia does not increase cardiovascular complications in the short term, indicating comparable cardiovascular safety profiles for lorlatinib and crizotinib.

2.2. Lorlatinib safety profile: overall considerations

Long-term safety data from the CROWN study show that hypercholesterolemia, hypertriglyceridemia, edema, weight gain and peripheral neuropathy are among the most observed AEs, with CNS AEs emerging in a consistent proportion of patients. Notably, certain AEs occurred less frequently in the CROWN study than in the phase I/II B7461001 study (hypercholesterolemia: 70% vs 96%, hypertriglyceridemia: 64% vs 90%, cognitive effects: 21% vs 27%), despite the shorter median lorlatinib exposure in the latter study (12.5 months vs 18.5 months in the CROWN study) [13,33]. Although these studies are not directly comparable, the discrepancies in AE rates may be due to the distinct settings of lorlatinib use, i.e., first-line therapy in the CROWN study, compared to the predominant second or later-line use in the B7461001 study, which may have been associated with accumulated toxicities from prior ALK TKIs treatment. Besides, patients' overall health status and cumulative dose and/or duration of previous treatments may also negatively impact the safety profile of subsequent therapies [34–37]. Given the absence of direct comparisons between AE profile in patients treated with lorlatinib in first- vs later lines, further analyses are warranted to confirm if its first-line use is associated with a lower risk of specific AEs, potentially offering a safer profile.

Intriguingly, the incidence of CNS AEs was found to be low (6.4%) among Chinese patients treated with second- or later line lorlatinib in a phase 2 study [38]. In the B7461001 study, while safety results were generally comparable between Asian and non-Asian patients, cognitive and mood effects were predominant in non-Asian (26.7% and 17.4%, respectively) compared to Asian populations (12.0% and 8.3%, respectively), while psychotic effects prevailed among Asian patients (12%, vs 2.5% in non-Asian patients) [39]. More recently, cognitive effects were reported in 25% of Asian patients during the five-year follow-up of the CROWN trial [40]. Thus, despite evidence suggesting a higher frequency of CNS AEs, particularly cognitive effects, in non-Asian populations, whether and how ethnic factors modulate such susceptibility remains to be elucidated. The onset of AEs varies according to the type of AE. Metabolic AEs like

hypercholesterolemia and hypertriglyceridemia often developed within two weeks of starting lorlatinib treatment [31,33]. Conversely, other side effects like weight gain and peripheral neuropathy typically appeared later (after median times of 112 days and 104.5 days, respectively) [31]. Concerning CNS AEs, cognitive effects first emerged after a median time of 154.5 days, with a range spanning from as early as 4 days to as late as 1307 days after treatment initiation [31].

The analysis of safety data from the CROWN study is still ongoing; the most recent follow-ups show rates of AEs consistent with those reported here [41].

2.3. Lorlatinib safety management

In clinical trials, AEs have been successfully managed through lorlatinib dose adjustments and/or temporary or permanent discontinuation [42]. In the updated CROWN analysis (36.7 months), any grade AEs led to lorlatinib temporary discontinuation, dose reduction and permanent discontinuation in 56%, 21% and 7% of patients, respectively. Various AEs caused lorlatinib permanent discontinuation at a similar rate (approximately 1% each) [31]. After 5 years of follow-up, the rates of dose reduction, temporary interruption and permanent discontinuation only slightly increased (62%, 23% and 11%, respectively) [15].

Special attention has been given to the management of hyperlipidemia and CNS AEs. After a median of 36.7 months, 22% of hyperlipidemia episodes and 59% of CNS AEs did not require any intervention. When intervention was needed, hyperlipidemia was preferentially managed with the sole use of concomitant medications (statins [pravastatin, pitavastatin, fluvastatin, rosuvastatin] or lipid-lowering agents, such as 3-hydroxy-3-methyl-glutaryl-coenzyme A [HMG CoA] reductase inhibitors, nicotinic acid, fibric acid derivatives, or ethyl esters of omega-3 fatty acids) without modifying lorlatinib dose (68% of cases). Conversely, only 14% of CNS AEs were managed with concomitant medications only [31].

First-line alectinib and lorlatinib safety data from the two phase III clinical trials ALEX and CROWN (initial analysis) were compared; although the rate of temporary discontinuation favored alectinib over lorlatinib (26% vs 56%, respectively), alectinib was associated with a similar rate of dose reduction (31% vs 32%, respectively), and a greater rate of permanent discontinuation compared to lorlatinib (15% vs 7%, respectively) [23]. Results from MAICs comparing the safety of lorlatinib (CROWN study) to alectinib (ALEX and ALESIA studies) and brigatinib (ALTA-1L study) revealed that the rates of AEs leading to dose reduction, interruption and discontinuation were similar between lorlatinib and alectinib. No significant differences were found between lorlatinib and brigatinib in terms of grade ≥3 AEs, dose reduction, interruption and discontinuation rates [24].

When compared to crizotinib, lorlatinib treatment was associated with higher rates of temporary interruptions (62% vs. 48%) and dose reductions (23% vs. 1%), while permanent discontinuation rates remained comparable between the two groups at 11% during the 5-year follow-up [15].

Remarkably, lorlatinib maintains its efficacy even when the dose is reduced. Chen et al. measured lorlatinib plasma exposure in patients who took part in the B7461001 study to investigate potential associations with objective response rate (ORR) and intracranial ORR. None of the two efficacy endpoints was significantly associated with lorlatinib exposure, implying that lorlatinib efficacy is preserved even if its dose is reduced [43]. These findings were corroborated in the updated CROWN analysis, where early lorlatinib dose reductions (within 16 weeks of treatment initiation) did not affect the 12-month PFS rate (84% in both patients undergoing lorlatinib dose reduction and those maintaining the initial dose) [32]. Data at 5 years further confirmed that median PFS and time to intracranial progression were not impacted by lorlatinib dose reduction [15].

3. Lorlatinib safety profile and management: data from studies in real-life

While several studies have investigated the effectiveness and safety of lorlatinib for ALK+ aNSCLC patients in real-world settings, its use as first-line therapy remains limited [44,45]. The Chinese study by Tian et al. has evaluated the effects of lorlatinib as a first-line treatment in the overall population [45]. In other studies, only few patients received first-line lorlatinib [46] and were often pooled with patients receiving later-line lorlatinib, precluding a distinct analysis of first-line efficacy and safety. The rate of lorlatinib-treated patients who experienced at least one AE of any grade varied greatly, with the lowest percentage at 49% over a median period of 25.3 months [47]. Hyperlipidemia, specifically hypercholesterolemia, was amongst the most frequent AEs (28%–81.5% of patients) [45–50], with severe (grade ≥3) cases reported in up to 15.4% of patients [45]. Non-CNS AEs, edema and weight gain were also observed [45,51].

CNS AEs in real-life occurred at a lower rate than in clinical trials, with 15.4% of patients experiencing any grade neurocognitive AEs after a median follow-up time from first-line lorlatinib of 9 months [45] and up to 5% and 1% patients experiencing grade ≥3 cognitive and mood effects after a median of 11.8 months, respectively [52]. An analysis of psychiatric AEs potentially related to each of the ALK TKIs currently approved for aNSCLC revealed that lorlatinib had the highest rate (2.8%), followed by brigatinib (1.2%) and alectinib (0.7%); ceritinib and crizotinib had lower percentages. These findings suggest that psychiatric AEs may be a potential class effect of ALK TKIs rather than being unique to lorlatinib [29].

Rates of lorlatinib dose reduction and discontinuation largely differed across studies.

The highest rate of lorlatinib permanent discontinuation was observed in 14% of patients [52], whereas other studies reported either no [48] or single cases [47,53] of discontinuation. In the study by Tian et al., 16.9% of patients required temporary suspension of first-line lorlatinib; after recovery from AEs, all patients resumed lorlatinib either at a reduced dose or at the original dose without experiencing other grade ≥3 AEs [45]. Dose reduction did not negatively influence either PFS or OS [54].

Although a direct comparison of safety data between real-life studies and clinical trials cannot be performed, some

discrepant results can be noticed. Compared to B7461001 study [33], lower rates of any grade hypercholesterolemia [46–50] and grade ≥3 hypercholesterolemia and hypertriglyceridemia [52] were observed in real-life. These discrepancies are likely due to the observational nature of real-life studies, which include broad patient population, varying treatment duration, and less stringent monitoring compared to clinical trials.

Post-marketing pharmacovigilance data offer crucial insight into rare or unexpected AEs associated with lorlatinib that may not have emerged during clinical trials or observational studies. A recent analysis of the FDA Adverse Event Reporting System (FAERS) identified new potential safety concerns such as thrombophlebitis migrans, radiation necrosis, and pericardial effusion, while also confirming pulmonary arterial hypertension (PAH) [55], already reported in a previous FAERS pharmacovigilance analysis [56]. These findings underscore the value of post-marketing data in complementing clinical trial evidence and highlight the need for clinicians to remain vigilant for rare but severe AEs during lorlatinib treatment.

4. Patients' experience with lorlatinib: data from patient-reported outcomes

Patients' quality of life (QoL) in clinical trials was evaluated using patient-reported outcomes (PROs); in the CROWN study, the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 (EORTC-QLQ-C30), EORTC QLQ-LC13 and the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaires were administered [13,57]. In the updated CROWN analysis (36.7 months), patients receiving lorlatinib significantly improved global QoL and emotional functioning scores compared with crizotinib-treated patients. Improvements in physical, role and social functioning favored lorlatinib, whereas the cognitive functioning scale favored crizotinib. Lorlatinib-treated patient improved multiple symptom scores (e.g., fatigue, nausea, insomnia, etc.) to a greater extent compared with crizotinib arm. Peripheral neuropathy was one of the symptoms more frequently reported by patients receiving lorlatinib compared to crizotinib [31].

In the previous *post hoc* analysis, of the initial CROWN data the impact of CNS AEs on EORTC QLQ-C30 Cognitive and Emotional Functioning domains was also investigated. Emotional Functioning scores improved over time in patients with and without CNS AEs. The occurrence of CNS AEs of any type was associated with a non-significant decline in cognitive functioning scores; not surprisingly, patients with cognitive effects had a more profound reduction of cognitive functioning scores compared with patients without [32].

QoL improvements were also observed in real-life [58]. In a Canadian study, the health utility score (a QoL estimate measured using the EQ-5D-5L questionnaire) significantly improved at 3 months from baseline and remained elevated at 6 and 12 months [58].

5. Management of lorlatinib AEs in clinical practice: current recommendations and suggestions from an Italian expert panel

A comprehensive pragmatic guide for managing lorlatinib-associated AEs has been published by Liu et al. [42].

The authors describe a four-steps approach: 1) prepare the patient (and the caregiver) before initiating lorlatinib treatment; 2) monitor the patient after starting lorlatinib treatment; 3) manage any emerging AEs according to current recommendations; 4) reassess patients periodically until symptoms improve. In agreement with the published recommendations, we provide additional suggestions to support HCPs according to the experience gained within the Italian healthcare system. The flowchart in Figure 2 illustrates the appropriate steps to manage safety concerns in the clinical practice, incorporating both published recommendations and the authors' insights.

5.1. Prepare

The "prepare" phase is crucial to inform patients and caregivers about the probability of developing lorlatinib-associated AEs, including the types of AEs that could occur and the related timeframes. Open communication between patients and healthcare providers (HCPs) is pivotal to pave the way for optimal safety management once the treatment starts. HCPs should perform baseline assessments, including neurological and cardiovascular evaluations, laboratory measurements, and evaluation of comorbidities and concurrent medications.

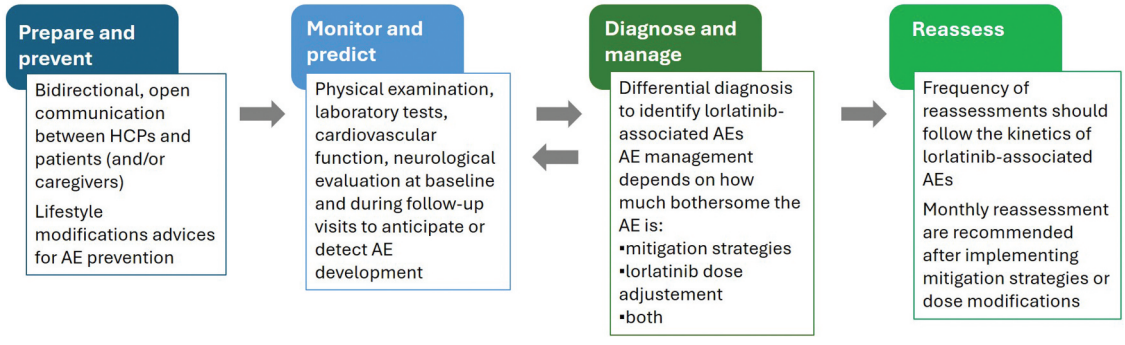

Figure 2. Recommended steps for appropriate management of lorlatinib-related safety concerns in the clinical practice. Text adapted from Liu et al. [42].
Abbreviations: AE: adverse event; HCP: healthcare professional.

Authors' suggestions: Establishing straightforward and bidirectional communication between the practitioner and the patient (and/or caregiver) before lorlatinib initiation is key to ensuring early identification of AEs. HCPs should encourage patients to improve their lifestyle by increasing physical activity and adopting a balanced diet, as preventive measures against possible AEs.

5.2. Monitor

Following lorlatinib treatment initiation, patients require careful monitoring at each follow-up visit to assess any potential AEs and determine their severity. In turn, patients should proactively report any change in cognitive, memory and speech abilities, and symptoms of peripheral neuropathy even before their scheduled visits.

Authors' suggestions: whenever possible, the occurrence of AEs should be anticipated by the clinician; any change in routine assessment results should trigger additional evaluations and/or interventions to limit the extent of the emerging AE. The use of telemedicine and/or telemonitoring tools should be enhanced to facilitate patient-practitioner remote communication and early symptom detection in between visits [42]. Given the rapid median time to the onset of hyperlipidemia and edema, early monitoring for signs of these conditions is crucial, especially during the initial two months of treatment. In contrast, CNS effects can manifest at various times, necessitating ongoing evaluation [42].

5.3. Manage

If an AE emerges, appropriate management should be initiated. In general, if AEs are mild and do not impact the patient's everyday life, they can be managed with mitigation strategies only. Nevertheless, lorlatinib should be reduced or interrupted in cases of CNS AEs and any other AE that the patient finds "bothersome," regardless of its actual grade of severity.

Authors' suggestions: a thorough differential diagnosis is essential for accurate identification and management of AEs. Symptoms directly related to lorlatinib treatment should be differentiated from those stemming from other factors, such as preexisting conditions.

As discussed above, the approach to managing AEs depends not only on their nature or severity but also on how burdensome the symptoms are, a factor that can be difficult to assess. Establishing a bidirectional communication between the patient and practitioner before treatment is of utmost importance for understanding the impact of symptoms and tailoring treatments accordingly.

Although lorlatinib is associated with a higher incidence of hyperlipidemia, it does not appear to increase the overall risk of cardiovascular events compared to crizotinib. Nevertheless, cardiovascular risk should be carefully assessed at baseline and monitored during treatment. Hypertension increases the overall cardiovascular risk and was found in 26% of lorlatinib-treated patients in the CROWN latest analysis [15]. Therefore, integrating regular blood pressure monitoring, both during clinic visits and at home, should be maximized to effectively identify and manage this side effect and its consequences.

5.4. Reassess

Patients experiencing AEs that require lorlatinib dose reduction should be reassessed monthly to determine the need for further dose adjustments [42].

Authors' suggestions: the kinetics of lorlatinib-associated AEs may provide a useful timeline for clinicians and patients, helping to guide monitoring visits and reassessments. For all AEs, the median time to onset occurs during the first 6 months after treatment initiation [41,42]. During this period, frequent blood tests and physical examinations should be performed. If necessary, lorlatinib dose should be paused and resumed at a lower dose, closely checking the impact on the patient's daily life.

5.5. Strategies to mitigate lorlatinib AEs

Figure 3 illustrates the typical timeline of lorlatinib AEs, while Table 2 and Figure 4 summarize the strategies to identify and manage the most common lorlatinib AEs [42]. Practical examples of weight gain and CNS management are shown in figure 5

Treatment with statins should be started as soon as lipid levels reach grade 1 toxicity (total cholesterol above the upper limit of normal [ULN] or triglyceride levels at or above 150 mg/dL) [42,59]. In cases of statin intolerance or insufficient response to maximal lipid-lowering therapies, referral to a cardiovascular or lipid specialist is recommended. Even if rarely described in the literature, clinicians should be aware of acute pancreatitis symptoms, as elevated triglyceride levels are associated with this condition [60].

Lorlatinib dose reduction should be implemented only after exhausting all options and in case of failure of maximal lipid-lowering therapy.

Concerning edema, clinicians should assess its impact on the patient's daily life rather than considering only its severity grade. Temporary lorlatinib interruption is advised in patients with bothersome symptoms; lorlatinib may be reintroduced at a reduced dose if symptoms improve.

A weight gain of 20% or more from baseline may warrant management strategies. Lorlatinib dose reduction is generally not advised unless lifestyle changes fail to alleviate weight-related discomfort.

In cases of peripheral neuropathy with mild symptoms, patients should adopt lifestyle changes and pharmacological interventions; bothersome neuropathy should prompt lorlatinib temporary interruption until symptoms improve.

Unlike other AEs, lorlatinib temporary interruption should be carried out as soon as CNS AEs emerge, even if not particularly bothersome. Patients with known risk factors for CNS AEs (with brain metastases, receiving brain radiation, with psychiatric illness, using neurotropic medications [61]) should be strictly monitored. If lorlatinib dose modification does not result in CNS symptom improvement, patients should be referred to psychiatrists or neurologists [42].

Potential drug–drug interactions with cytochrome P450 (CYP) 3A inducers (e.g., rifampicin) or inhibitors (e.g.,

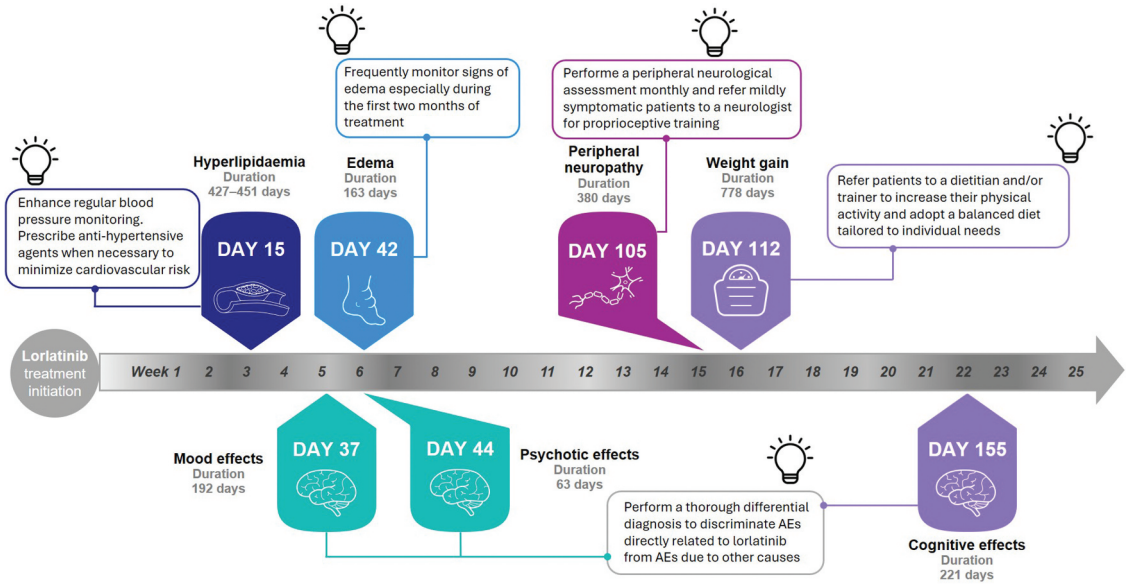

Figure 3. Typical timeline of lorlatinib AEs and recommended strategies to manage them. Times-to-first occurrence and duration for each AE are expressed as median values [42]. Authors' advices are indicated. Modified from Liu et al. [42].

Abbreviation: AE: adverse event.

Table 2. Strategies to mitigate lorlatinib most common AEs in the clinical practice (adapted from [42]).

AE	Non-pharmacological approaches	Pharmacological approaches
Hyperlipidemia (including hypercholesterolemia, hypertriglyceridemia, elevated and severely elevated lipid levels)	Dietary changes are unlikely to be effective in managing hyperlipidemia	• Preferred statins to administer in combination with lorlatinib: pitavastatin, pravastatin, rosuvastatin (minimal interaction with CYP3A4). • Lipid-lowering agents: ezetimibe, fibrates/fish oil. • PCSK9 inhibitors may be used in statin-intolerant patients • In case of acute pancreatitis, the management is based on symptom severity • Long-term treatment should aim at reducing triglyceride levels
Edema	• Assess the presence of underlying conditions (cardiac, renal and thyroid disorders) • Compression bandage, lifting the area above the heart, exercise, reduction of salt intake, physiotherapy	• Diuretics may be used • Involvement of other specialists (i.e., cardiologists, endocrinologists) to evaluate other causes and solutions
Weight gain	Nutritional and dietary counseling, exercise	• Semaglutide and other incretins may be used upon expert approval and monitoring of potential side effects
Peripheral neuropathy	Carpal tunnel syndrome may be alleviated by use of a night splint	• Vitamin B1, vitamin B6, and medications like gabapentin or pregabalin might be used to alleviate symptoms.
CNS AEs (cognitive, mood, speech, psychotic)	• Address any underlying causes of neurocognitive or psychiatric impairment and seek specialist (psychiatrist, neurologist) evaluation • Practice mindfulness or meditation techniques, and engaging in cognitive behavioral therapy	• Lorlatinib should be interrupted and eventually reintroduced at a lower dose • If CNS symptoms are severe and persistent, other pharmacological treatments should be prescribed by a specialist

itraconazole) have also been highlighted [33,42]. Strong CYP3A inhibitors should be avoided as they may increase lorlatinib plasma availability, thus raising the rate and severity of lorlatinib-associated AEs. If the use of moderate CYP3A inducers or inhibitors is necessary, lorlatinib dose should be either increased or decreased, respectively [42].

Authors' suggestions: anti-hypertensive agents (e.g., angiotensin-converting enzyme [ACE] inhibitors, sartans, calcium channel blockers) should be used when necessary to minimize cardiovascular risk. If patients are refractory to the anti-hypertensive treatment, or in case of high cardiovascular risk, patients should be referred to a cardiologist as soon as possible.

To manage weight gain, patients should consult with a dietitian or personal trainer to obtain tailored recommendations based on individual needs.

AEs should be preferentially managed with mitigation strategies, eventually combined with lorlatinib dose reduction.

Toxicity	How bothersome is the toxicity?			Reassess regularly until stable/improved
	Not bothersome	Mildly/moderately	Severly	
Peripheral neuropathy Edema	Lifestyle modification Physical training exercises	Temporarily stop lorlatinib; then continue with the same dose or reduce by -1DL (75 mg)	**Temporarily stop lorlatinib; then continue with -1DL (75mg) or -2DL (50mg) if one previously managed mild/moderate event occurred**	If worse reduce till -2DL If stable or better continue with the same dose (no escalating dose strategy)
CNS (cognitive, mood, speech, psychotic)	Discuss and reassure. Alternate psychological support·	Temporarily stop lorlatinib; then continue with -1DL (75mg)		
Cardiovascular toxicity	Monitor cardiovascular signs (BP/ECG)			
Weight gain	Lifestyle modification and check for other concomitant causes			

Figure 4. Overview of the management of selected symptomatic AEs. Modified from Liu et al. [42].

Abbreviations: 1DL: one dose level; 2DL: two dose levels; AE: adverse event; BP: blood pressure; CNS: central nervous system; ECG: electrocardiogram.

Management of lorlatinib-induced weight gain

Prepare	Monitor (at 2 months)		Reassess every 2 months until stable/improved
• Inform the patient • Perform a nutritional screening • Educate on proper food hygiene • Recommend the control of previous endocrine pathologies • Refer to a nutritionist	**No weight gain**	Continue with the same dose Monitor weight every 2 months	If uncontrolled weight gain (further >10% body weight) and exclusion of any other concomitant metabolic disorder Temporarily stop lorlatinib; then continue with -1DL
	Weight gain >5%≤10%	Continue with the same dose Refer to a nutritionist Suggest physical exercise	
	Weight gain > 10%	Temporarily stop lorlatinib; then continue with the same dose Refer to a nutritionist Refer to a psychologist Suggest physical exercise	

Management of lorlatinib-induced CNS effect

Prepare	Monitor (at 1 month)		Reassess monthly until stable/improved
• Assess risk factors (brain mets, brain RT, psychiatric illness, neurotropic medication) • Advise patients and caregivers • Early assessment and interview of caregivers and patient's interview on a regular basis	**G2-3**	**Temporary** dose **interruption** → Resume at -25 mg reduced dose	**Brain imaging** in case of lacking improvement within few days **Further** -25 mg dose reduction **Psychiatrists/neurologists** consultation in case of lacking improvement with mitigation strategies
	G4	**Permanent discontinuation**	

Figure 5. Practical examples of management strategies along time for lorlatinib-induced weight gain and CNS effect. Modified from Liu et al. [42].

Abbreviations: 1DL: one dose level; AE: adverse event; CNS: central nervous system; G: grade.

Lorlatinib interruption should be carefully considered and limited to specific cases (i.e., CNS effects). Consultation with other specialists should be considered before discontinuing the treatment.

6. Conclusions

This narrative review of safety data from clinical trials shows that most lorlatinib-associated AEs are generally predictable, manageable and reversible, especially when appropriate monitoring and supportive strategies are consistently applied. However, the conclusions drawn here are based on expert opinion and are not based on a systematic review or data meta-analysis. The perspectives presented reflect the clinical experience of Italian experts, which may limit generalizability to broader international contexts and diverse healthcare systems. We also acknowledge that the evidence on lorlatinib-associated AE management will continue to evolve as more long-term and real-world data become available, potentially leading to a redefinition of the suggested management approaches.

Despite these limitations, the long-term efficacy data from the CROWN study along with indirect comparisons and real-world studies support the view that lorlatinib's safety profile represents a point of attention for in-depth analysis, without precluding the use of lorlatinib as first-line treatment of ALK+ aNSCLC, unless for clear contraindications to its use.

The benefits of lorlatinib generally outweigh its risks, as evidenced by the infrequent need for dose modification or interruption in clinical trials and real-life studies. Pragmatic strategies offer guidance to ensure patient engagement and minimize AEs impact. Preventing and anticipating AEs should be a priority during lorlatinib treatment. HCPs should establish effective, open communication with patients and proactively recommend prevention strategies through lifestyle modifications to minimize AEs occurrence.

By closely monitoring patients, clinicians should aim to predict the occurrence of AEs and intervene as appropriate. Cardiovascular risk should be assessed at baseline and during treatment through regular blood pressure and blood lipid measurements, with consultation with a cardiologist if necessary. Nutritional counseling and physical activity advice should be sought in case of concern for weight gain. Collaboration with other specialists should be considered in case of CNS AEs, which may require lorlatinib dose adjustments. If feasible, clinicians should prioritize lorlatinib dose reduction over discontinuation given its continued efficacy at lower doses. Lorlatinib should be selected among other TKIs on a case-by-case basis, following careful patient evaluation.

7. Future perspective

Over the next years, the treatment landscape for ALK+ NSCLC is expected to evolve significantly, with a growing number of potent and safe ALK TKIs. A growing body of real-world evidence will provide valuable insights into the long-term safety profiles of lorlatinib and other ALK TKIs, while future studies will focus on identifying AEs predictive biomarkers. Digital health tools are expected to play a critical role in real-time AE monitoring, enabling early detection and timely intervention. Additionally, artificial intelligence (AI) will enhance the ability to predict AE risks and optimize patient management. A stronger focus on patient-centered care, including prevention strategies, lifestyle interventions and multidisciplinary support, will ensure that treatment-related toxicities are effectively managed and patient outcomes maximized.

Author contributions

Andrea Ardizzoni, Diego Cortinovis, Giulia Pasello, Filippo de Marinis: conceptualization, data curation, methodology, formal analysis, writing – original draft, writing – review & editing. Bruno Gori, Amedeo Nuzzo: conceptualization, methodology, funding acquisition, project administration, resources, writing – original draft, writing – review & editing. All authors approved the final version to be submitted.

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