Long-Term Safety and Management of Adverse Events Associated With Lorlatinib in *ALK*-Positive Metastatic NSCLC: A Fictional Case Study

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Rearrangements of the anaplastic lymphoma kinase (*ALK*) gene are present in about 3% to 7% of patients with non–small cell lung cancer (NSCLC) and are the key drivers of cancer cell proliferation in *ALK*-positive NSCLC. ALK tyrosine kinase inhibitors (TKIs) are potent oral inhibitors of the abnormal ALK protein and are standard first-line treatments for patients with *ALK*-positive metastatic NSCLC (mNSCLC). Lorlatinib is a brain-penetrant, third-generation ALK TKI that was approved by the US Food and Drug Administration in 2018 for the second- or third-line treatment of patients with *ALK*-positive mNSCLC and in 2021 for first-line treatment, based on the results of the phase III CROWN study (NCT03052608). The recent 5-year results of the CROWN study showed that median progression-free survival had yet to be reached in the lorlatinib group, corresponding to the longest progression-free survival reported with any single-agent molecular targeted treatment in advanced NSCLC and all metastatic solid tumors (Solomon et al., 2024). These results, along with the extended intracranial efficacy and consistent safety profile of long-term lorlatinib treatment, are unprecedented in patients with *ALK*-positive mNSCLC. This Grand Rounds article summarizes the efficacy, safety, and tolerability of lorlatinib after 5 years and includes a fictional patient case to demonstrate how advanced practice providers contribute to personalized patient care and the identification and management of adverse events.

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CASE STUDY

The patient case described is fictional and does not represent actual events with an actual patient; this patient is representative of those enrolled in the CROWN study and presented for educational purposes only.

Susan, a 61-year-old White female never smoker, was diagnosed with anaplastic lymphoma kinase (*ALK*)–positive stage IV/metastatic non–small cell lung cancer (mNSCLC). Her Eastern Cooperative Oncology Group performance status was 1. Her medications included atorvastatin (Lipitor), lisinopril (Zestril), and citalopram (Celexa). Presenting symptoms, medical history, and diagnostic information are in Figure 1.

Susan was prescribed lorlatinib (Lorbrena) 100 mg orally once daily. Due to potential drug-drug interactions (DDIs) with lorlatinib, atorvastatin 20 mg was changed to rosuvastatin (Crestor) 10 mg, and citalopram was monitored to determine the need for dose increase since DDIs may result in subtherapeutic levels.

Before beginning lorlatinib, the advanced practice provider (APP) educated Susan and her husband about common adverse events (AEs; Table 1) and the importance of reporting them early to begin management strategies, including lorlatinib dose modification, lifestyle modifications, or additional medications. The APP emphasized to her husband the importance of early identification of central nervous system (CNS) symptoms, which Susan may not recognize herself. They discussed the potential for lorlatinib to increase appetite, which could result in weight gain, and the importance of a balanced diet and regular exercise routine. Before starting lorlatinib, Susan's baseline weight was measured; laboratory tests, including a fasting lipid panel, were conducted; and a psychological history was taken by the APP. To ensure prompt detection of AEs, follow-up visits were scheduled approximately 2, 4, and 8 weeks after the initiation of lorlatinib.

Non–small cell lung cancer (NSCLC) is the most common type of lung cancer, comprising approximately 85% of lung cancer cases (Wang et al., 2023). A subset of patients with NSCLC (3%–7%) have chromosomal rearrangements of ALK (Guo et al., 2022), which are key drivers of cancer cell growth in *ALK*-positive NSCLC. These patients have a high incidence of brain metastases, with approximately 24% to 29% having brain metastases at diagnosis and > 50% developing them after 3 years (Camidge et al., 2018; Rangachari et al., 2015; Shaw et al., 2020).

ALK-positive NSCLC is sensitive to treatment with ALK tyrosine kinase inhibitors (TKIs; Shaw et al., 2020), oral targeted therapies that slow or stop cancer cell growth by targeting and blocking the abnormal ALK protein. Biomarker testing at diagnosis is crucial (Hirsch & Kim, 2024), as > 50% of patients with mNSCLC have tumors containing targetable genetic alterations, such as *ALK* rearrangements. Current guidelines recommend broad tissue- and/or plasma-based molecular profiling that identifies all biomarkers in a single assay (Riely et al., 2024); one such assay is next-generation sequencing. While waiting for biomarker results can be stressful, results are critical to optimize treatment selection and patient outcomes.

Several ALK TKIs are approved for the treatment of *ALK*-positive mNSCLC, including crizotinib (Xalkori), alectinib (Alecensa), brigatinib (Alunbrig), ceritinib (Zykadia), ensartinib (Ensacove), and lorlatinib (Lorbrena; Table 2). Lorlatinib is a third-generation ALK TKI designed to penetrate the blood-brain barrier for CNS activity and has activity against *ALK* resistance mutations (Shaw et al., 2020). The CROWN study, evaluating lorlatinib vs. crizotinib for treatment-naive *ALK*-positive mNSCLC, showed that median progression-free survival (PFS) remained unreached in the lorlatinib group after 5 years of follow-up (Solomon et al., 2024).

Despite significant advances in the field, many patients with *ALK*-positive mNSCLC (25%–41%) do not receive second-line therapy, largely due to disease progression, suggesting that the most effective treatment should be used in the first-line setting (Bauman et al., 2024).

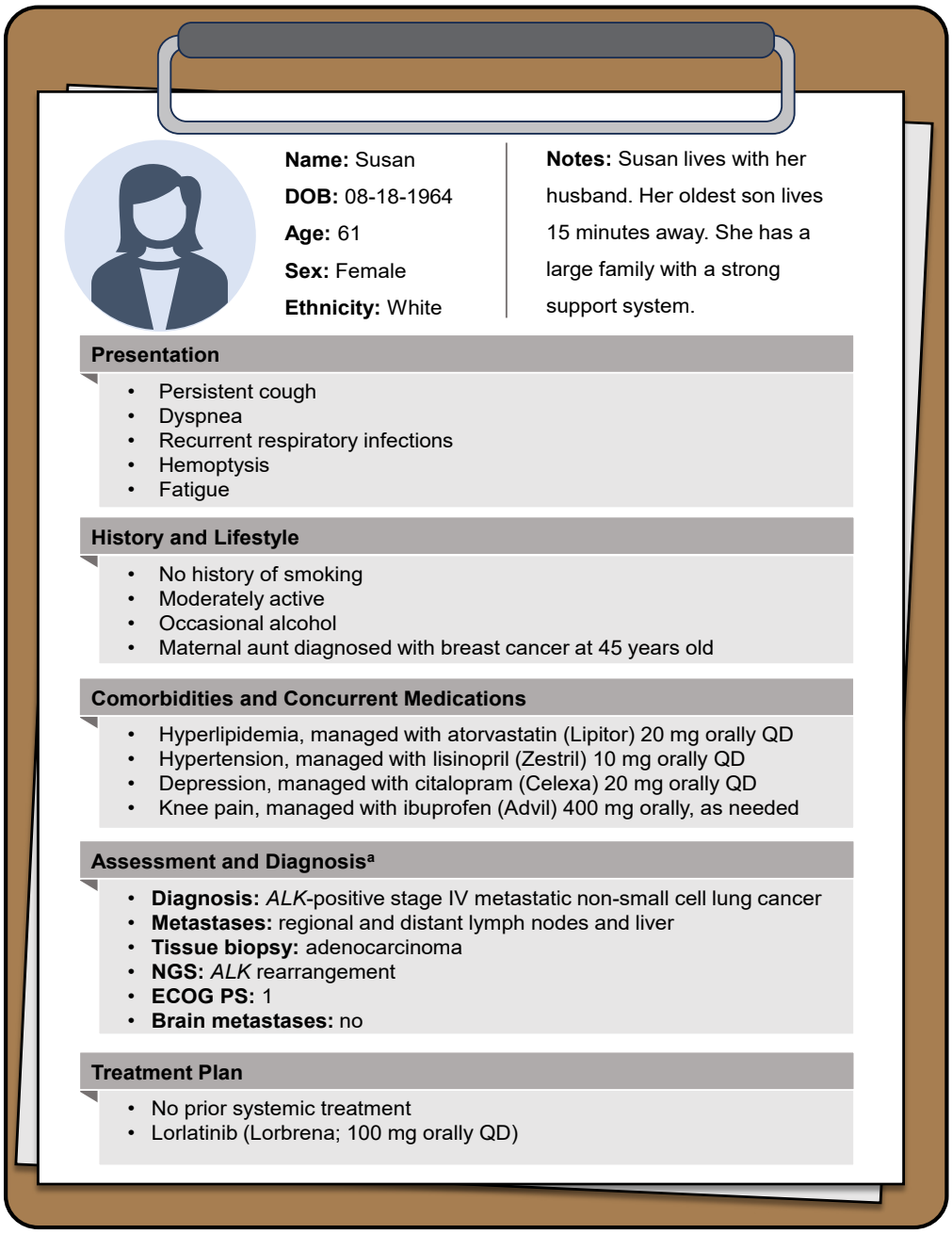

Figure 1. Summary of the fictional case study. *ALK* = anaplastic lymphoma kinase; CNS = central nervous system; DOB = date of birth; ECOG = Eastern Cooperative Oncology Group; NGS, next-generation sequencing; PS = performance status; QD = once daily.
[a]A computed tomography scan of the chest, abdomen, and pelvis revealed a mass in the lower left lobe of the lung, enlargement of left supraclavicular and mediastinal lymph nodes, and liver metastasis. Gadolinium contrast–enhanced magnetic resonance imaging of the brain revealed no CNS metastasis. Endobronchial ultrasound-guided percutaneous fine-needle aspiration of a level 2 supraclavicular lymph node and pathological examination revealed adenocarcinoma histology. Broad-based biomarker testing was performed based on current guidelines (Riely et al., 2024); NGS revealed an *ALK* rearrangement in the tumor. Based on these findings, the diagnosis of *ALK*-positive metastatic non-small cell lung cancer was established.

Table 1. All-Causality AEs Occurring in ≥ 20% of Patients Treated With Lorlatinib in the CROWN Study (*n* = 149)

	Any grade	Grade 3	Grade 4
Any AE, *n* (%)	149 (100)	95 (64)	20 (13)
Hypercholesterolemia[a]	108 (72)	30 (20)	2 (1)
Hypertriglyceridemia[a]	99 (66)	25 (17)	12 (8)
Edema[a]	85 (57)	6 (4)	0
Peripheral neuropathy[a]	65 (44)	2 (1)	0
Weight increased	65 (44)	34 (23)	0
Fatigue[a]	45 (30)	2 (1)	0
Arthralgia	41 (28)	1 (1)	0
Cognitive effects[a,b]	41 (28)	5 (3)	0
Hypertension	39 (26)	18 (12)	0
Anemia	37 (25)	6 (4)	0
Diarrhea	34 (23)	3 (2)	0
Dyspnea	34 (23)	5 (3)	0
Headache	33 (22)	0	0
Mood effects[a,c]	31 (21)	2 (1)	0
Cough	30 (20)	0	0
Pyrexia	30 (20)	1 (1)	0

Note. AE = adverse event; SOC = system organ class. Information from Solomon et al. (2024).
[a]This category comprised a cluster of AEs that may represent similar clinical symptoms or syndromes.
[b]Cognitive effects include amnesia, cognitive disorder, disturbance in attention, memory impairment, mental impairment, confusional state, delirium, and disorientation.
[c]Mood effects include affective disorder, affect lability, agitation, anger, anxiety, bipolar I disorder, depressed mood, depression, depressive symptom, euphoric mood, irritability, mood altered, mood swings, and stress.

LORLATINIB FOR *ALK*-POSITIVE mNSCLC: EFFICACY

The phase III CROWN study enrolled 296 treatment-naive patients with *ALK*-positive mNSCLC who were randomized 1:1 to receive oral lorlatinib 100 mg once daily (*n* = 149) or crizotinib 250 mg twice daily (*n* = 147; Shaw et al., 2020). Interim analysis demonstrated that lorlatinib improved PFS and intracranial response vs. crizotinib but was associated with a higher incidence of grade 3/4 AEs (72% vs. 56%, respectively), primarily due to altered lipid levels, although rates of permanent discontinuation due to AEs were low in both groups (7% vs. 9%).

A post hoc analysis after 5 years of follow-up reported updated investigator-assessed efficacy outcomes (Table 3; Solomon et al., 2024). With a median follow-up for PFS of 60.2 months with lorlatinib and 55.1 months with crizotinib, median PFS was not reached (NR; 95% CI = 64.3–NR) and 9.1 months (95% CI = 7.4–10.9), respectively (hazard ratio [HR], 0.19; 95% CI = 0.13–0.27); the probability of being progression free was 60% and 8% at 5 years. The confirmed objective response rate was 81% (95% CI = 73–87) with lorlatinib and 63% (95% CI = 54–70) with crizotinib. Intracranial response with lorlatinib was durable, with median time to intracranial progression NR (95% CI = NR–NR) vs. 16.4 months (95% CI = 12.7–21.9) with crizotinib (HR, 0.06; 95% CI = 0.03–0.12). In the lorlatinib group, the probability of being free from intracranial progression was 92% at 5 years. Benefits in PFS and intracranial time to progression were observed in patients with and without baseline brain metastases. This PFS represents an unprecedented outcome with any single-agent molecular targeted treatment in mNSCLC and across all metastatic solid tumors.

Table 2. FDA-Approved Targeted Therapies for Adults With ALK-Positive mNSCLC

Generation of ALK TKI	Therapy	FDA approval and milestones
First	Crizotinib (Xalkori)	• Received accelerated FDA approval as ≥ 2L therapy[a] in 2011, becoming the first approved ALK TKI in this patient population • Became the 1L standard of care after demonstrating superior efficacy as 1L therapy vs. chemotherapy in the phase III PROFILE 1014 study (NCT01154140)
Second[b]	Alectinib (Alecensa)	• Received accelerated FDA approval as 2L therapy[c] in 2015, based on two pivotal phase II studies[d] • Received FDA approval as 1L therapy in 2017, based on the phase III ALEX study (NCT02075840)
	Brigatinib (Alunbrig)	• Received accelerated FDA approval as 2L therapy[c] in 2017, based on the phase II ALTA study (NCT02094573) • Received FDA approval as 1L therapy in 2020, based on the phase III ALTA-1L study (NCT02737501)
	Ceritinib (Zykadia)	• Received FDA approval as 2L therapy[c] in 2014, based on the phase I ASCEND-1 study (NCT01283516) • Received FDA approval as 1L therapy in 2017, based on the phase III ASCEND-4 study (NCT01828099)
	Ensartinib (Ensacove)	• Received FDA approval as 1L therapy in 2024, based on the phase III eXALT3 study (NCT02767804)
Third	Lorlatinib (Lorbrena)	• Received accelerated FDA approval as 2L or 3L therapy[e] in 2018, based on the pivotal phase I/II study (NCT01970865) • Received FDA approval as 1L therapy in 2021, based on the phase III CROWN study (NCT03052608)

Note. 1L = first line; 2L = second line; 3L = third line; ALK = anaplastic lymphoma kinase; FDA = US Food and Drug Administration; mNSCLC = metastatic non-small cell lung cancer; TKI = tyrosine kinase inhibitor. Information from Blackhall & Cappuzzo (2016); Fox Chase Cancer Center (2014); Genentech (2015); Novartis Pharmaceuticals Corporation (2021); Pfizer (2011, 2018, 2021); Shaw et al. (2020); Solomon et al. (2014); US Food and Drug Administration (2017a, 2017b, 2017c, 2020, 2024).

[a]In patients previously treated with one or more systemic therapy (Malik et al., 2014). Approval was originally based on a phase II study (PROFILE 1005) and a part 2 expansion cohort of a phase I study (Study 1001; Pfizer, 2011).

[b]Several second-generation ALK TKIs with improved intracranial activity were developed following crizotinib (Wei et al., 2023; Wu et al., 2016).

[c]In patients who have had progression on or are intolerant of crizotinib.

[d]NP28761 was a North American phase II study, and NP28673 was a global phase I/II study; both evaluated the safety and efficacy of alectinib in patients whose disease progressed on crizotinib.

[e]In patients whose disease progressed on crizotinib and at least one other ALK TKI for mNSCLC or whose disease progressed on alectinib or ceritinib as the first ALK TKI for mNSCLC.

PREPARING THE PATIENT AND CAREGIVER FOR LORLATINIB: ROLE OF THE APP

Advanced practice providers (APPs) are integral throughout a patient's cancer care. They conduct a full assessment of the patient's medical condition and history at baseline. Careful consideration of many factors, including medical history, concurrent medications, support system, adherence, medical literacy, and patient preferences, is crucial in selecting the optimal, personalized treatment. Before lorlatinib initiation, APPs educate patients and caregivers on critical medication information, such as proper dosage, administration, DDIs, common AEs, and when and how to report AEs so that the dose can be modified if necessary. As patients may remain on therapy for a prolonged period, prompt identification, reporting, and management of AEs is paramount to tolerability and maintaining quality of life.

Critical aspects of lorlatinib education include a review of potential AEs. As most patients will experience elevated lipids, patients should be prepared for regular monitoring of lipid levels and potential need for a lipid-lowering agent. Increased appetite and resultant weight gain should also be discussed, including strategies to maintain a healthy diet and regular exercise. Details concerning CNS AEs should be provided in plain language so that patients and caregivers know what to look for and understand that some changes will

Table 3. Summary of Efficacy of Lorlatinib (Lorbrena) in the CROWN Study at 5 Years[a]

ITT population	**Lorlatinib (*n* = 149)**	**Crizotinib (*n* = 147)**
Duration of follow-up for PFS, median (95% CI), months	60.2 (57.4–61.6)	55.1 (36.8–62.5)
PFS, median (95% CI), months	NR (64.3–NR)	9.1 (7.4–10.9)
HR (95% CI)	0.19 (0.13–0.27)	
ORR (95% CI), %	81 (73–87)	63 (54–70)
Best overall response, *n* (%)		
Complete response	15 (10)	3 (2)
Partial response	105 (70)	89 (61)
Stable disease	16 (11)	38 (26)
Progressive disease	8 (5)	7 (5)
Not evaluable	5 (3)	10 (7)
DOR, median (95% CI), months	NR (NR–NR)	9.2 (7.5–11.1)
IC TTP, median (95% CI), months	NR (NR–NR)	16.4 (12.7–21.9)
HR (95% CI)	0.06 (0.03–0.12)	
Patients with baseline brain metastases	**Lorlatinib (*n* = 35)**	**Crizotinib (*n* = 38)**
PFS, median (95% CI), months	NR (32.9–NR)	6.0 (3.7–7.6)
HR (95% CI)	0.08 (0.04–0.19)	
IC TTP, median (95% CI), months	NR (NR–NR)	7.2 (3.7–11.0)
HR (95% CI)	0.03 (0.01–0.13)	
Patients without baseline brain metastases	**Lorlatinib (*n* = 114)**	**Crizotinib (*n* = 109)**
PFS, median (95% CI), months	NR (64.3–NR)	10.8 (9.0–12.8)
HR (95% CI)	0.24 (0.16–0.36)	
IC TTP, median (95% CI), months	NR (NR–NR)	23.9 (16.4–30.8)
HR (95% CI)	0.05 (0.02–0.13)	

Note. DOR = duration of response; HR = hazard ratio; IC = intracranial; ITT = intention-to-treat; NR = not reached; ORR = objective response rate; PFS = progression-free survival; TTP = time to progression. Information from Solomon et al. (2024).
[a]Efficacy endpoints were by investigator assessment for the 5-year analysis.

be subtle and may not be noticeable to the patient. For example, cognitive effects could manifest as changes in memory or attention, confusion, forgetfulness, or disorientation. Changes in mood include anxiety, depression, changes in affect, irritability, and agitation. Speech changes could include slurred or slowed speech or difficulties articulating, and psychotic changes include visual or auditory hallucinations and delusion.

Reassuring patients and caregivers that AEs are generally manageable with dose adjustments, lifestyle modifications, and concurrent medications helps to instill confidence. Throughout the patient's care, APPs are available for support and continually monitor AEs, which is particularly important given lorlatinib's unique safety profile (Liu et al., 2024). Comprehensive patient care involves a collaborative team of experts. In some cases, consultation with dieticians, psychologists, and cardiologists may be beneficial.

LORLATINIB: SAFETY AND TOLERABILITY

Long-term lorlatinib safety outcomes remained consistent with earlier analyses, with no new safety signals (Solomon et al., 2024). Median treatment duration was 57.0 months. All-cause AEs led to lorlatinib dose interruptions in 62% of patients, dose reductions in 23%, and permanent discontinuation in 11% (Table 4). Treatment-related permanent discontinuations occurred in 5% of patients, all in the first 26 months.

Table 4. Dose Modifications of Lorlatinib Due to All-Cause AEs in the CROWN Study

Lorlatinib dose modifications for AE management	Lorlatinib (*n* = 149)
Dose interruptions, *n* (%)	92 (62)
Most common AEs, %	
Hypertriglyceridemia[a]	8
Pneumonia	8
Cognitive effects[b]	6
COVID test positive	6
Edema[c]	5
Peripheral neuropathy[d]	5
Mood effects[e]	5
Dose reductions, *n* (%)	34 (23)
Most common AEs, %	
Edema[f]	7
Hypertriglyceridemia[g]	4
Cognitive effects[h]	3
Mood effects[i]	3
Peripheral neuropathy[j]	3
Permanent discontinuation, *n* (%)	16 (11)
Most common AEs, %	
Cognitive effects[k]	1
Cardiac failure	1

Note. AE = adverse event; SMQ = Standardized MedDRA Query. Information from Solomon et al. (2024). Data on file.
[a]Hypertriglyceridemia leading to dose interruptions included any event with a preferred term of hypertriglyceridemia (5%) and increased blood triglycerides (3%).
[b]Cognitive effects leading to dose interruptions included any event with a preferred term of disturbance in attention (2%), cognitive disorder (1%), delirium (1%), memory impairment (1%), amnesia (< 1%), and disorientation (< 1%).
[c]Edema leading to dose interruptions included any event with a preferred term of peripheral edema (5%) and generalized edema (1%).
[d]Peripheral neuropathy leading to dose interruptions included any event with a preferred term belonging to SMQ peripheral neuropathy, such as peripheral motor neuropathy (1%), peripheral sensory neuropathy (1%), dysesthesia (< 1%), muscular weakness (< 1%), neuromyopathy (< 1%), peripheral neuropathy (< 1%), and neurotoxicity (< 1%).
[e]Mood effects leading to dose interruptions included any event with a preferred term of anxiety (2%), depression (1%), anger (< 1%), bipolar I disorder (< 1%), and depressive symptoms (< 1%).
[f]Edema leading to dose reductions included any event with a preferred term of peripheral edema (5%), generalized edema (1%), and edema (1%).
[g]Hypertriglyceridemia leading to dose reductions included any event with a preferred term of hypertriglyceridemia (2%) and increased blood triglycerides (2%).
[h]Cognitive effects leading to dose reductions included any event with a preferred term of amnesia (< 1%), cognitive disorder (< 1%), disorientation (< 1%), disturbance in attention (< 1%), and memory impairment (< 1%).
[i]Mood effects leading to dose reductions included any event with a preferred term of anger (< 1%), bipolar I disorder (< 1%), depressed mood (< 1%), irritability (< 1%), and psychomotor retardation (< 1%).
[j]Peripheral neuropathy leading to dose reductions included any event with a preferred term of paresthesia (1%), peripheral neuropathy (< 1%), and peripheral sensory neuropathy (< 1%).
[k]Cognitive effects leading to permanent discontinuation included any event with a preferred term of confusional state (1%).

Health-care providers should reassure patients that dose reductions did not impact PFS or intracranial time to progression in the CROWN study (Solomon et al., 2024). The median time to onset and duration of AEs with lorlatinib varied, with any-grade hyperlipidemia having a median time to onset of 0.5 months (Figure 2). Except for weight gain, higher grade toxicities (grade ≥ 3) did not persist when managed properly.

LORLATINIB: MANAGEMENT STRATEGIES

Advanced practice provider–led education of patients and caregivers on effective management strategies facilitates safe administration of lorlatinib and supports adherence. Adverse events associated with lorlatinib are reversible with dose interruption or reduction (Bauer et al., 2019; Liu et al., 2024). Health-care providers will determine the optimal dose for each patient based on individual tolerability.

Management depends on AE grade and, importantly, considers the impact on patient quality of life. General recommendations for management of AEs with lorlatinib are outlined in Figure 3 (Liu et al., 2024). Some mild AEs do not require intervention if they are not troubling the patient, or may be managed with mitigation strategies rather than dose interruption or reduction (Liu et al., 2024).

Drug-drug interactions may result in an increase or decrease in the therapeutic effect of a drug or may increase drug toxicity and impact treatment outcomes and adherence (Riechelmann & Del Giglio, 2009). Lorlatinib is metabolized primarily by CYP3A4 and is a moderate inducer of CYP3A4 and P-glycoprotein (Chen et al., 2024; Pfizer Labs, 2023; Reed et al., 2020). Potential DDIs should be considered, and patients should discuss concurrent medications with their physician and pharmacist before and during treatment with lorlatinib (Figure 4).

CASE STUDY CONTINUED: EFFICACY OUTCOMES AND MANAGEMENT OF AEs

During Susan's toxicity assessment 2 weeks after initiating lorlatinib, blood tests showed elevated lipid levels, reflecting grade 2 hypercholesterolemia and hypertriglyceridemia. Rosuvastatin was increased to 20 mg once daily. At her 4-week assessment, no new AEs were detected, and lorlatinib was continued at 100 mg daily.

At Susan's 2-month follow-up appointment, she had +1 pitting edema bilaterally, and the APP reviewed helpful interventions (i.e., raising legs above the heart, wearing compression stockings, limiting dietary sodium, and increasing activity levels). Although diuretics were not indicated at this visit, Susan was encouraged to contact the office about any clinical worsening in case additional interventions or a referral to a lymphedema clinic may be warranted. Susan experienced continued low-level fatigue and was referred to physical therapy to learn exercises to increase mobility, endurance, and strength. Despite experiencing edema and mild fatigue, Susan reported noticeable improvement in her baseline respiratory symptoms. Full restaging with computed tomography scans were performed, which demonstrated partial response, and lorlatinib 100 mg daily was continued.

Prior to her 4-month appointment, Susan's husband noticed increased irritability, which differed from her baseline temperament. He brought this to Susan's attention, and they contacted the APP. Lorlatinib was held until Susan's irritability resolved and was then restarted at a reduced dose of 75 mg once daily.

At her 4-month appointment, Susan reported that regular exercise had improved both her energy level and her lower extremity edema. At this time she also experienced new nonpainful neuropathic sensory changes in her hands and feet at night, consistent with peripheral neuropathy. The APP explained that peripheral neuropathy can occur with lorlatinib and be exacerbated by edema and weight gain. She was encouraged to continue regular exercise and limit sodium intake to manage the edema, which could indirectly improve the neuropathy (Liu et al., 2024). She was told that if the peripheral neuropathy continued or worsened, lorlatinib could be further reduced to 50 mg. Despite her increase in physical activity, Susan had gained 10 lbs since her last visit. The APP reminded her that increased appetite is a common AE with lorlatinib and encouraged her to maintain a regular exercise routine and offered to refer her to a nutritionist, if desired.

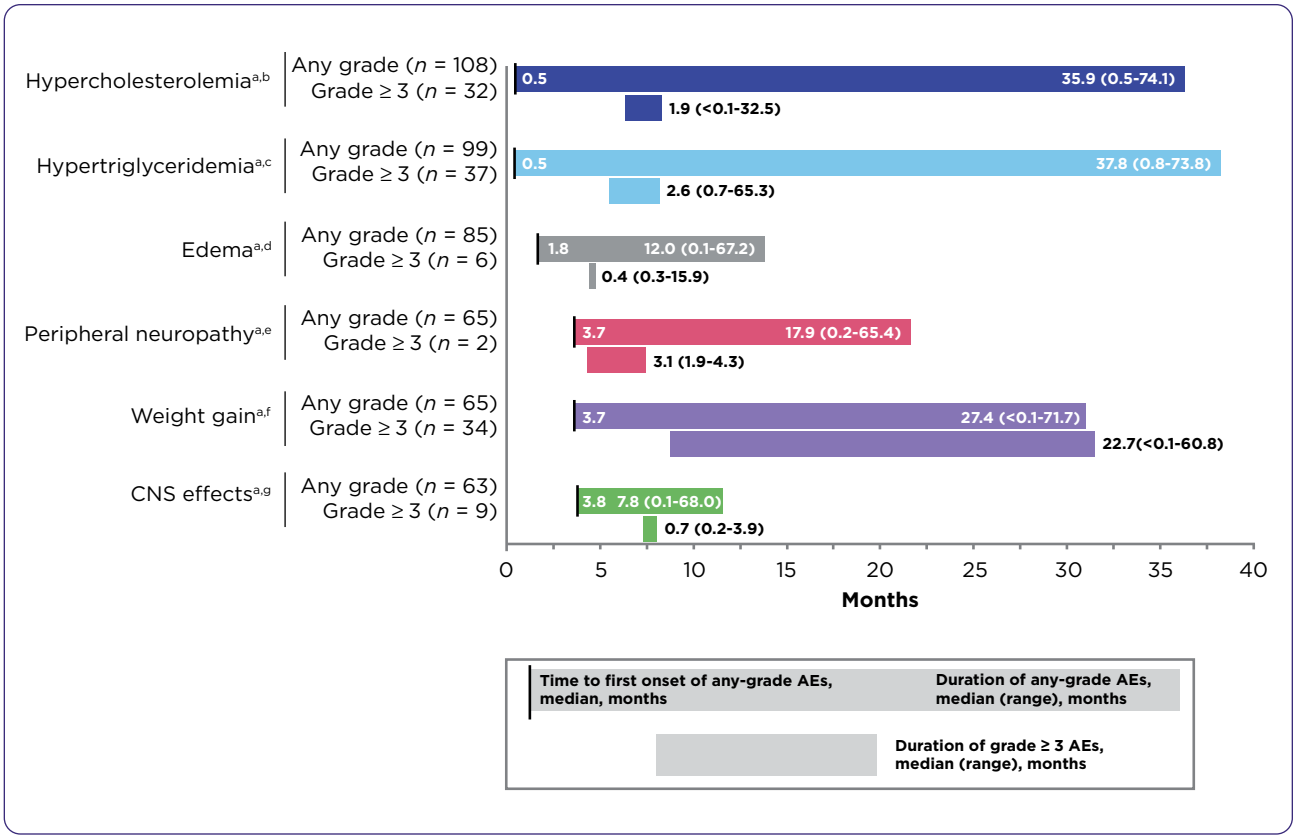

Figure 2. Median time to onset and duration of all-cause AEs. AE = adverse event; CNS = central nervous system; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query.
[a]MedDRA v26.1 coding dictionary applied.
[b]Hypercholesterolemia was any event with a preferred term of blood cholesterol increased or hypercholesterolemia.
[c]Hypertriglyceridemia was any event with a preferred term of blood triglycerides increased or hypertriglyceridemia.
[d]Edema was any event with a preferred term of edema, peripheral edema, generalized edema, peripheral swelling, or swelling.
[e]Peripheral neuropathy was any event with a preferred term that belonged to SMQ peripheral neuropathy.
[f]Weight gain was any event with a preferred term of weight increased.
[g]CNS effects were any events from the following cluster terms: cognitive effects, mood effects, speech effects, and psychotic effects.

At her 5-month appointment, the AEs Susan had previously reported had been mitigated with the interventions initiated; therefore, follow-up visits were scheduled every 3 months. After 5 years, Susan continues on lorlatinib and has remained in good health without disease progression.

DISCUSSION

The unprecedented efficacy of lorlatinib for patients with *ALK*-positive mNSCLC, highlighted by the 5-year results of the CROWN study, has increased awareness of the need to better understand lorlatinib's safety profile and therapy management principles. Various publications have described lorlatinib's safety profile and management, including a pragmatic approach that focuses on how bothersome AEs are for patients and caregivers (Bauer & Bertino, 2022; Bauer et al., 2019; Liu et al., 2024).

First-line lorlatinib demonstrated long-term systemic and intracranial antitumor activity in treatment-naive patients, with the median PFS and median time to intracranial progression not reached after 5 years of follow-up (Solomon et al., 2024).

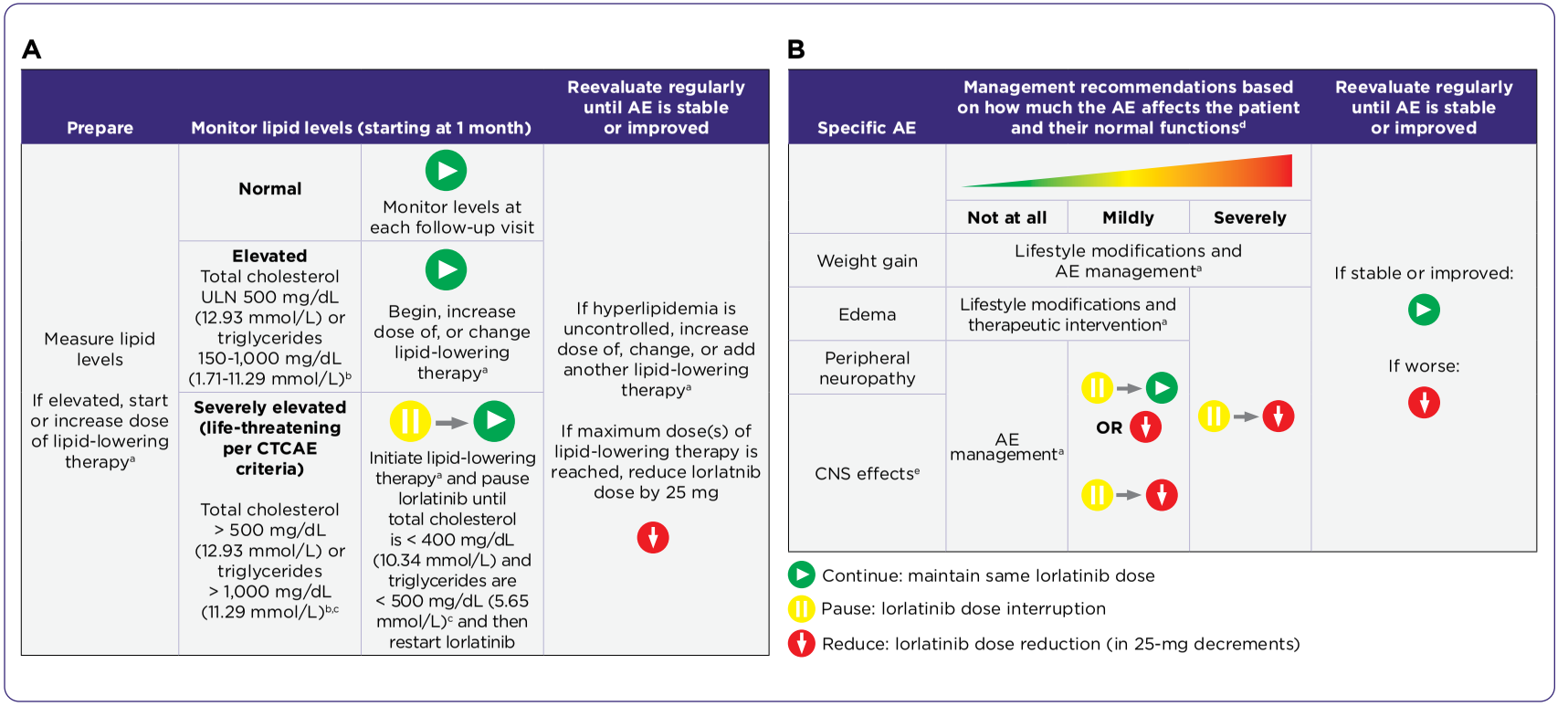

Figure 3. Management of AEs with lorlatinib. Information from Liu et al. (2024). (A) Management of lorlatinib-induced hyperlipidemia and (B) management of nonlaboratory AEs, including weight gain, edema, peripheral neuropathy, and CNS effects. Reprinted from Liu G, et al. Lung Cancer. 2024:191:107535. Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).
AE = adverse event; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.
[a]Mitigation strategies are discussed in the body of the manuscript.
[b]Values obtained from Alonso et al., 2019.
[c]Cholesterol and triglyceride threshold values can be modified based on overall cardiovascular risk and life expectancy.
[d]As severity increases, add management recommendations from left to right. For example, for edema that is severely bothersome, consider lifestyle modifications and therapeutic intervention, then dose interruption, and finally dose reduction. Note that severity of AEs is subjective; if a patient experiences a mildly bothersome AE that is functionally debilitating or functionally detrimental, this may be interpreted as being severely bothersome after discussion with patient and health-care provider. This is particularly true for CNS toxicities, for which severely bothersome may equate to any CNS functional detriment.
[e]Includes cognitive, mood, speech, and psychotic effects. Central nervous system AEs 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 resolution of symptoms is not recommended.

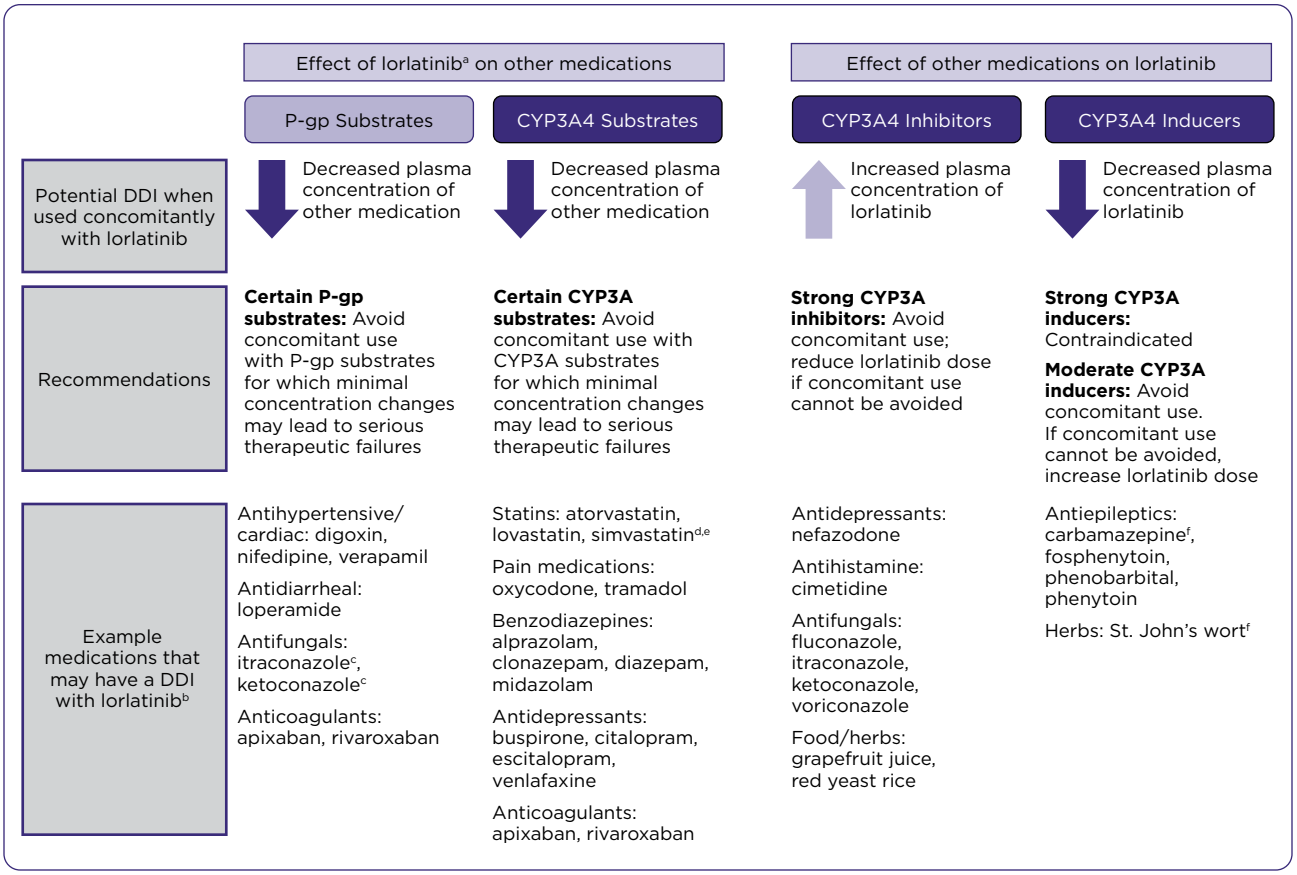

Figure 4. Summary of medications prescribed for common AEs with potential DDIs with lorlatinib.
AE = adverse event; CYP3A4 = cytochrome P450 3A4; DDI = drug-drug interaction; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9. Information from Dorababu et al. (2009); Fung et al. (2012); Gulikers et al. (2022); Kane & Lipsky (2000); Marok et al. (2023); Pfizer Labs (2023); Reed et al. (2020); UpToDate (2025); Wang et al. (2002); Wessler et al. (2013).

[a]Lorlatinib is a substrate and moderate inducer of CYP3A4.

[b]The examples given are not all inclusive. A complete DDI assessment should be conducted for lorlatinib and all concomitant medications and herbs.

[c]Also functions as a P-gp inhibitor.

[d]Alternative medications with lower DDI potential that may be taken concurrently with lorlatinib to manage hyperlipidemia include fluvastatin, pravastatin, rosuvastatin, and pitavastatin.

[e]Advanced practice providers may also consider other add-on agents that can improve lipid panel results, such as ezetimibe (preferred add-on therapy for LDL-C reduction and recent acute coronary syndrome due to cost considerations and easy oral administration), PCSK9 inhibitors (may be added to statin plus ezetimibe in very high-risk patients who are not at target LDL-C or non–HDL-C levels), or bile acid sequestrants (may be used as an alternative to ezetimibe with an expected 10%–15% reduction in LDL-C but should be avoided in those with triglyceride concentrations > 300 mg/dL).

[f]Strong CYP3A4 inducer.

Since lorlatinib may be used to control disease long term, it is important to understand AE timing and prompt identification and management. The safety profile of lorlatinib is generally manageable, with most grade 3/4 AEs being laboratory abnormalities such as hypercholesterolemia and hypertriglyceridemia; these AEs are primarily managed with lipid-lowering statins and led to dose interruption or dose reduction in 8% and 4% of patients, respectively. For patients with elevated lipids despite statins, the addition of another lipid-lowering medication, such as ezetimibe (Zetia) or fenofibrate (Tricor), may be considered (Liu et al., 2024).

Although Susan's age is the median in the CROWN study, APPs should consider the strategies to manage younger patients as well. They should discuss fertility preservation, with referrals to fertility specialists as needed. Patients may also benefit from psychological referrals for difficulty coping, assistance with continuing employment and health insurance coverage, and physical therapy to support an active lifestyle and caring for their family. Patient advocacy groups, including ALK Positive, LUNGevity, and the GO2 Foundation, offer excellent resources and support for patients and their families.

The CROWN 5-year data demonstrated lorlatinib's efficacy in patients with and without baseline brain metastases. In patients with measurable or nonmeasurable baseline brain metastases, the intracranial objective response rate was 60% and median duration of intracranial response was not reached (Solomon et al., 2024). Given the increased mortality associated with brain metastases (Bazhenova et al., 2024), these are important considerations. Advanced practice providers treating patients with brain metastases should ensure that patients, family members, and caregivers are educated on the potential CNS effects of lorlatinib and encouraged to promptly notify providers of any symptom changes. Central nervous system imaging, such as magnetic resonance imaging, is repeated with each set of body scans to ensure CNS disease is controlled, and CNS assessments (i.e., headache, vision, and balance assessments) may be conducted. Brain radiotherapy can occasionally be avoided in patients treated with lorlatinib, given the drug's potent CNS penetrance (Gafer et al., 2019; Murakami et al., 2024).

Tyrosine kinase inhibitors have dramatically altered the outlook for patients with *ALK*-positive mNSCLC and offer patients improved outcomes compared with chemotherapy. Given the durability of ALK TKIs, long-term management and support of patients are crucial. Advanced practice providers are essential members of the health-care team, ensuring optimal patient care and early identification and management of AEs. Education and clear communication between the APP and patient and caregiver are crucial to achieve the goal of disease management with continued treatment, while maintaining quality of life. ●

Data Sharing Statement

On request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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Disclosure

Ms. Krueger has received speaker fees/honoraria from Pfizer. Dr. Alejandro is an employee of Pfizer. Ms. McDonald has received consulting fees, speaker fees/honoraria, and travel support from Pfizer and has served on an advisory board for Pfizer. Dr. Lewis has served on advisory boards for Bristol Myers Squibb, Daiichi Sankyo, Eisai, and Johnson & Johnson. The other authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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