Kinetics and Management of Adverse Events Associated With Lorlatinib After 5 Years of Follow-Up in the CROWN Study

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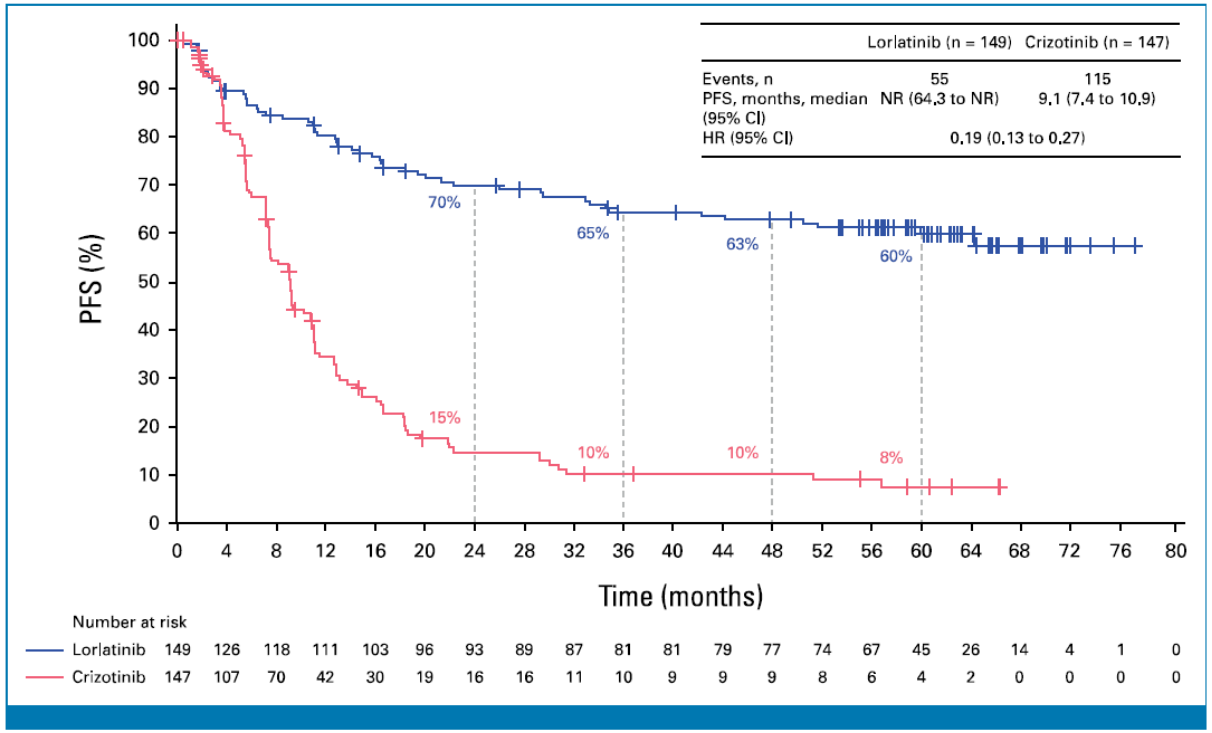
CROWN: A Randomized Global Phase 3 Study (NCT03052608)

- Lorlatinib is approved for the treatment of patients with metastatic *ALK*+ NSCLC[1]
- In the CROWN study, with a median duration of follow-up for PFS of 60.2 months, median PFS was NR (95% CI, 64.3 months-NR) with lorlatinib[2]
- Because lorlatinib has a unique safety profile,[3,4] in this post hoc analysis, we present kinetics of selected AEs from the CROWN study after 5 years of follow-up to suggest optimized therapy management strategies



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AE, adverse event; ALK, anaplastic lymphoma kinase; HR, hazard ratio; NR, not reached; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

1. Lorbrena (lorlatinib). Prescribing information. Pfizer Inc; 2021. Accessed June 10, 2024. https://labeling.pfizer.com/ShowLabeling.aspx?id=11140. 2. Solomon BJ, et al. *J Clin Oncol.* 2024:JCO2400581. 3. Shaw AT, et al. *N Engl J Med.* 2020;383:2018-2029. 4. Liu G, et al. *Lung Cancer*. 2024;191:107535.

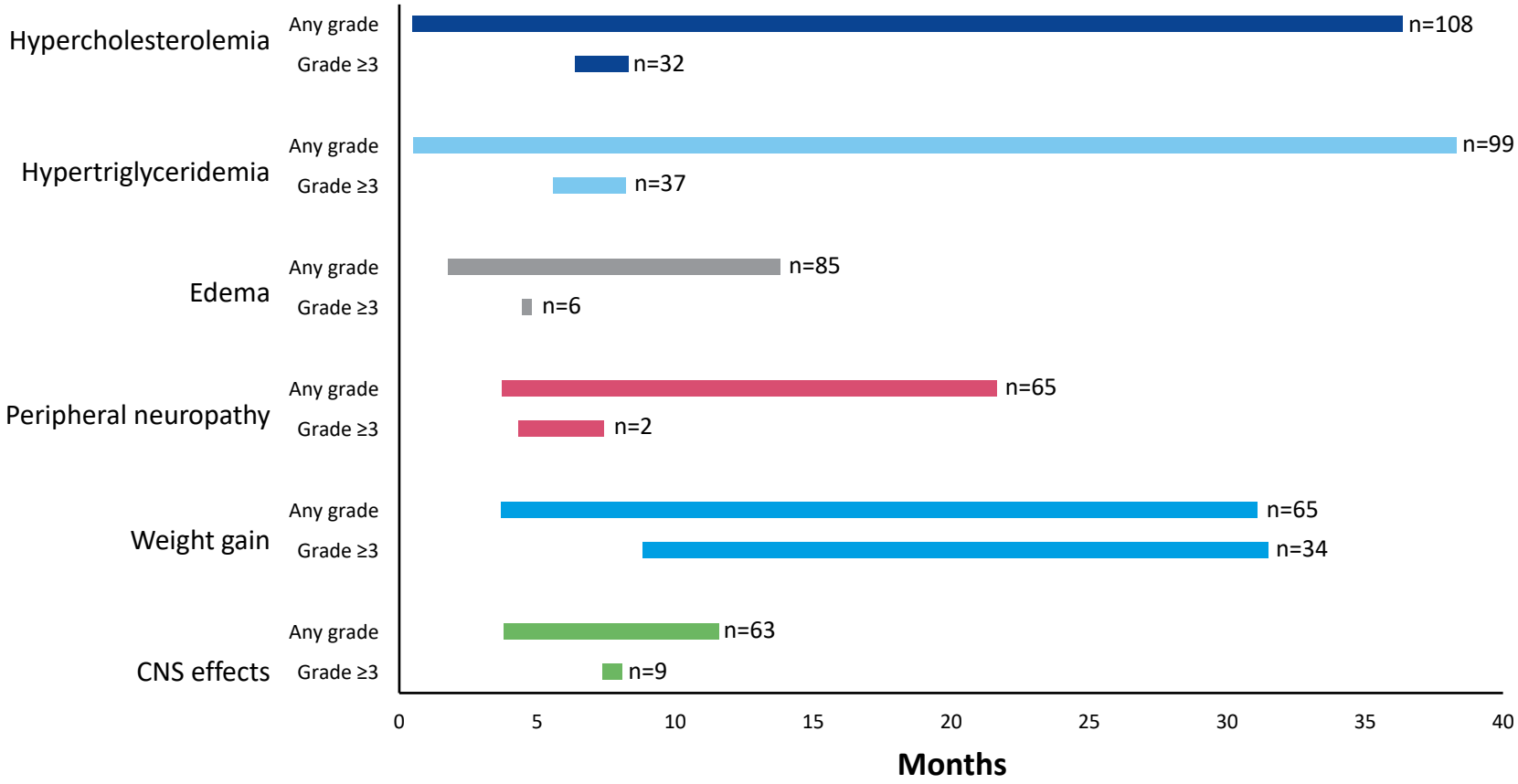
Safety Key Takeaways After 5 Years of Follow-up

- At the data cutoff of Oct 31, 2023, treatment was ongoing in 50% of patients treated with lorlatinib[1]
- This post hoc analysis suggests that with long exposure to lorlatinib, no new safety signals emerged and treatment discontinuation remained low after 5 years of follow-up
- With lorlatinib, all-cause AEs led to permanent discontinuation in 11% of patients; in 5%, these AEs were treatment related[1]
  - All other patients were efficiently managed with dose reductions or interruptions
- In patients who had dose reduction (n=49), median time to first dose reduction was 21.6 weeks (range, 2.1-281.9)
- Dose reduction did not affect efficacy of lorlatinib[1]

AE, adverse event.
1. Solomon BJ, et al. *J Clin Oncol*. 2024 May 31:JCO2400581.

Time to Onset and Duration of AEs

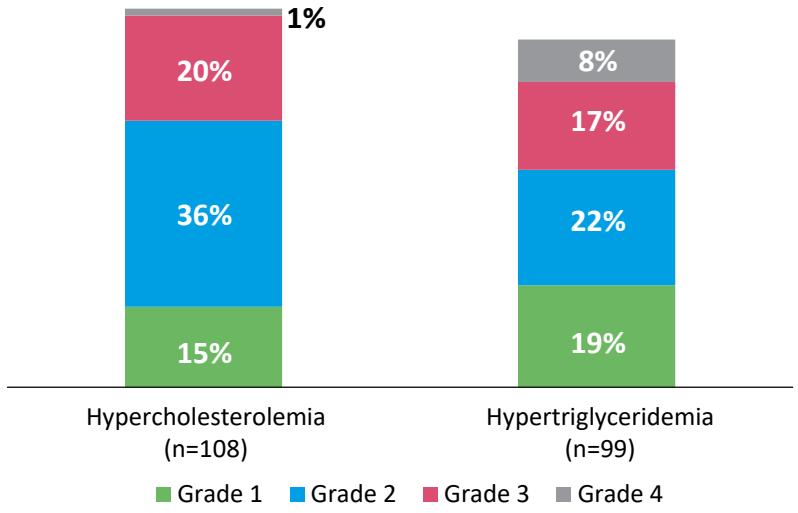
- For hyperlipidemia, time to onset of any-grade AEs was 15 days, and duration was ≈37 months; time to onset of grade ≥3 AEs was ≈6 months
- For peripheral neuropathy, weight gain, and CNS effects, time to onset of any-grade AEs was ≈4 months, and duration was 18, 27, and 8 months, respectively
- Except for weight gain, duration of grade ≥3 AEs was ≤3 months



AE, adverse event; CNS, central nervous system.

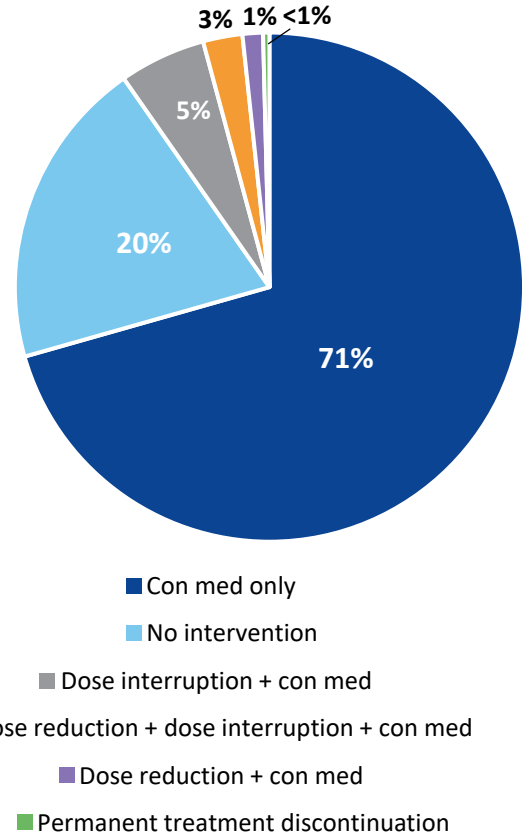
Most Hyperlipidemia Events were Managed by Con Med

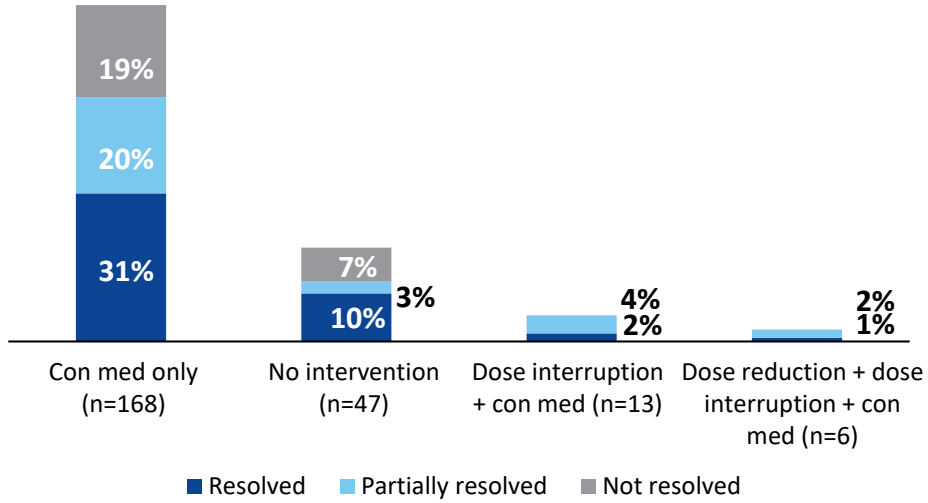
Lorlatinib (N=149)



- Hypercholesterolemia and hypertriglyceridemia were observed in the majority of the patients treated with lorlatinib

Total hyperlipidemia events (n=238)





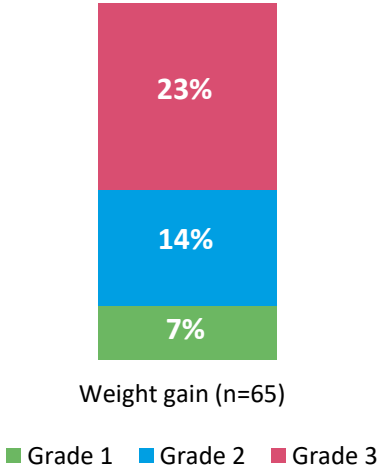
- Most of the hyperlipidemia events were managed and controlled by the use of lipid-lowering agents[1]
- Pitavastatin, pravastatin, or rosuvastatin should initially be considered based on their low involvement with specific CYP450 enzymes that can interact with lorlatinib (e.g., CYP3A4)[2]
- Overall, 45% of hyperlipidemia events resolved; permanent treatment discontinuation occurred in only 1 patient

con, concurrent; med, medication.

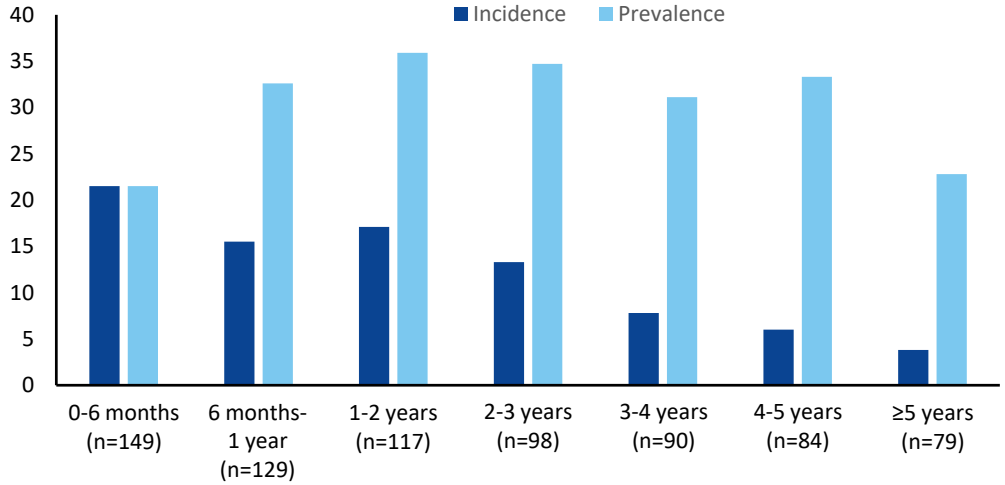
1. Liu G, et al. *Lung Cancer*. 2024;191:107535. 2. Neuvonen PJ, et al. *Clin Pharmacol Ther.* 2006;80:565–581.

Weight Gain Events Occurred in 44% of Patients

Lorlatinib (N=149)

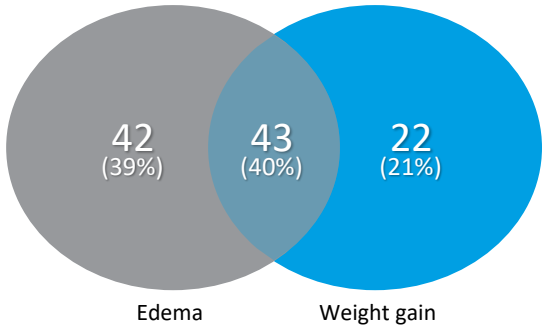


	Grade 2/3 weight gain (n=55)	No grade 2/3 weight gain (n=94)
Baseline body weight, median (range), kg	64 (43-88)	64 (32-105)



- Weight gain was observed in almost half of the patients treated with lorlatinib; baseline body weight did not influence subsequent weight gain
- Incidence and prevalence of weight gain did not increase over time
- Weight gain and edema seem to correlate only in a fraction of patients, suggesting different pathogenetic mechanisms for these AEs

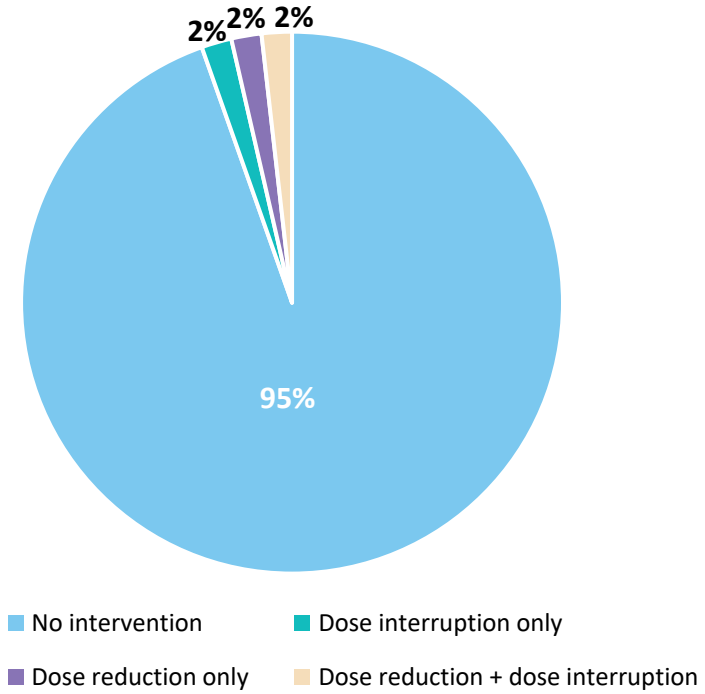
Patients with edema and/or weight gain (n=107)

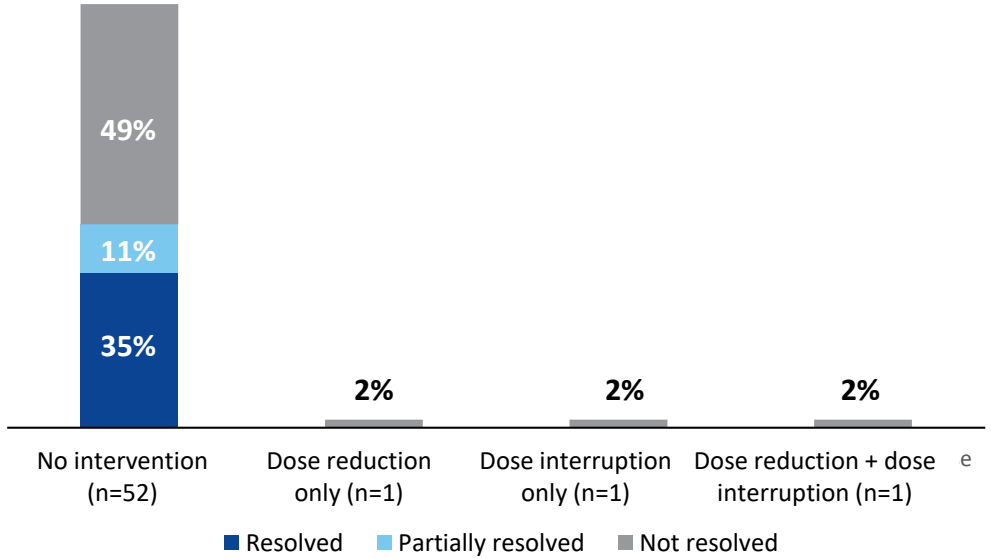


AE, adverse event.

Most Weight Gain Events Were Managed With Lifestyle Modifications

Total weight gain events (n=55)

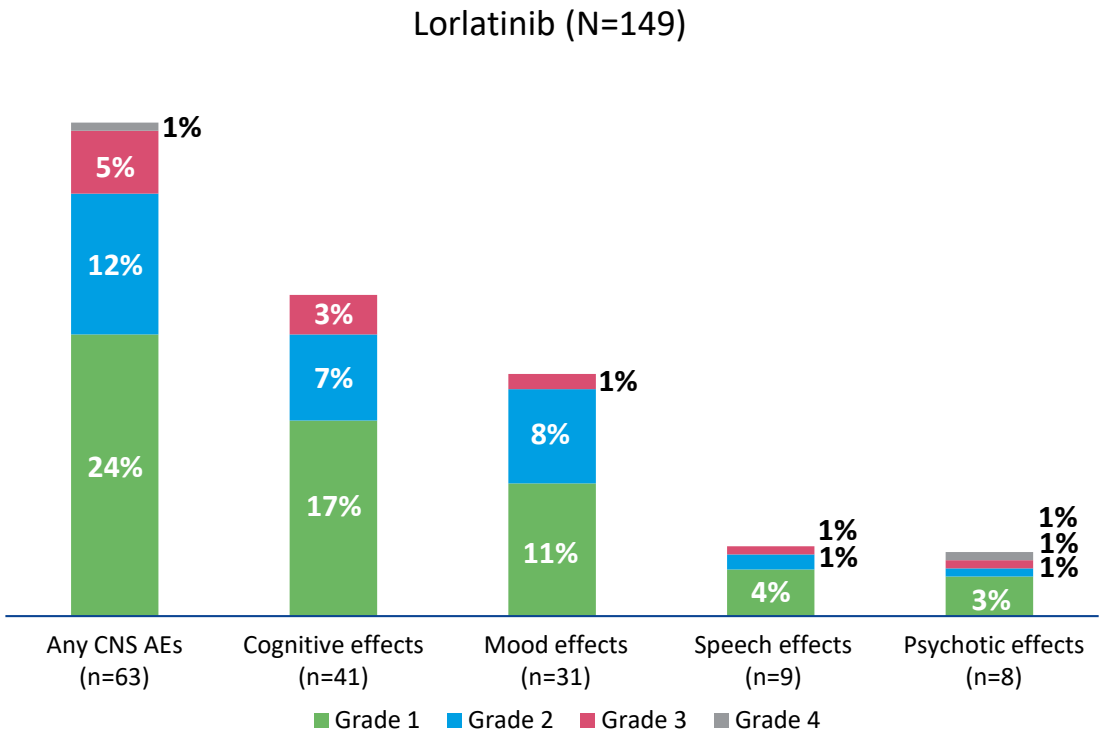




- Most weight gain events were managed without any intervention; lifestyle modifications are generally recommended[1]
- Overall, 35% of all weight gain events resolved with no intervention at all

1. Liu G, et al. *Lung Cancer*. 2024;191:107535.

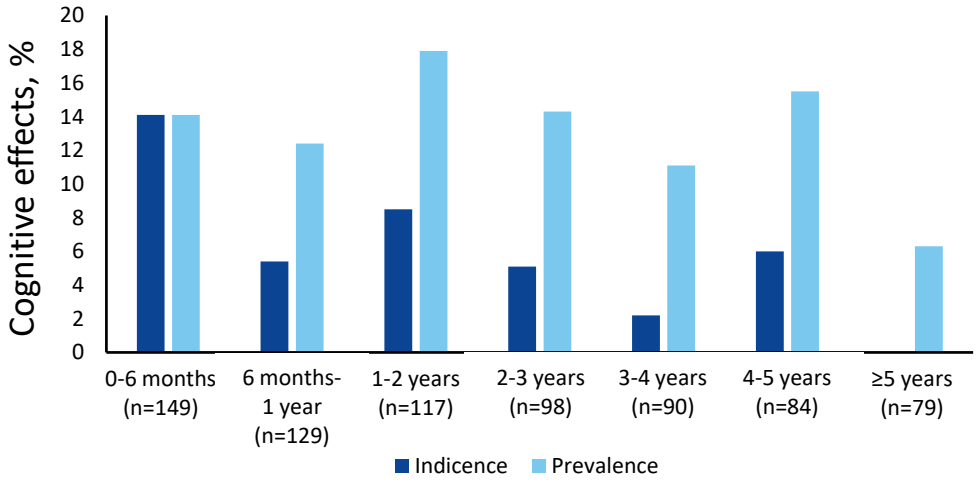
Most CNS AEs Were of Grade 1/2 Severity

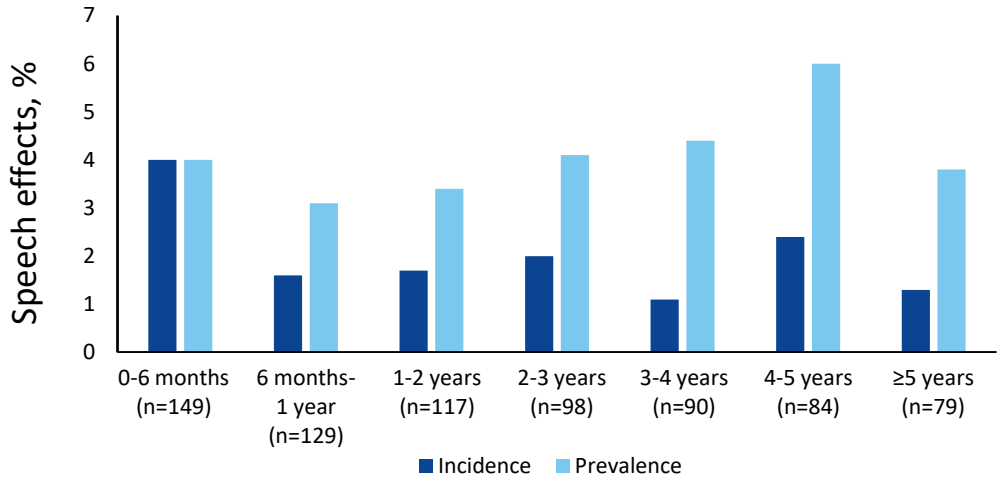


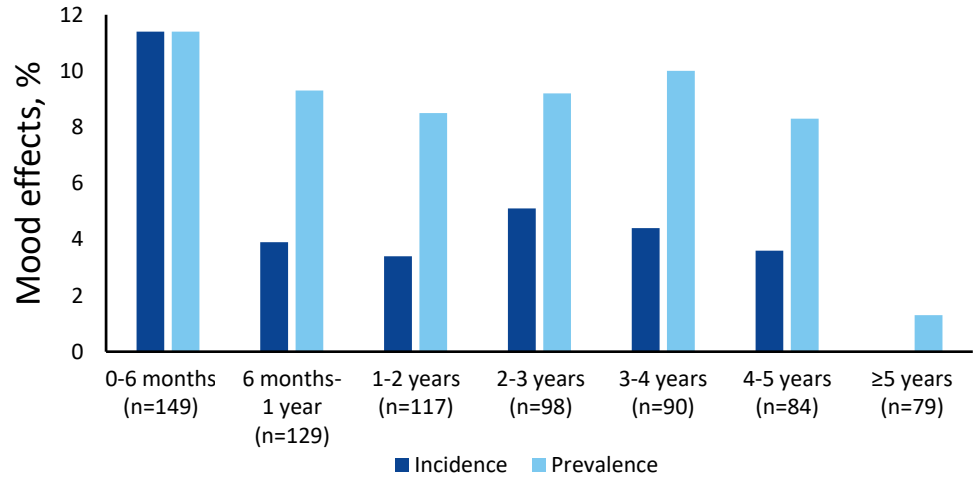
- All-causality CNS AEs occurred in 42% of patients, the majority of which (86%) were of grade 1/2 severity[1]
- As previously reported, CNS AEs occurred in 67% of patients who had prior brain radiotherapy (n=9) and 41% of patients without prior brain radiotherapy (n=140)[1]

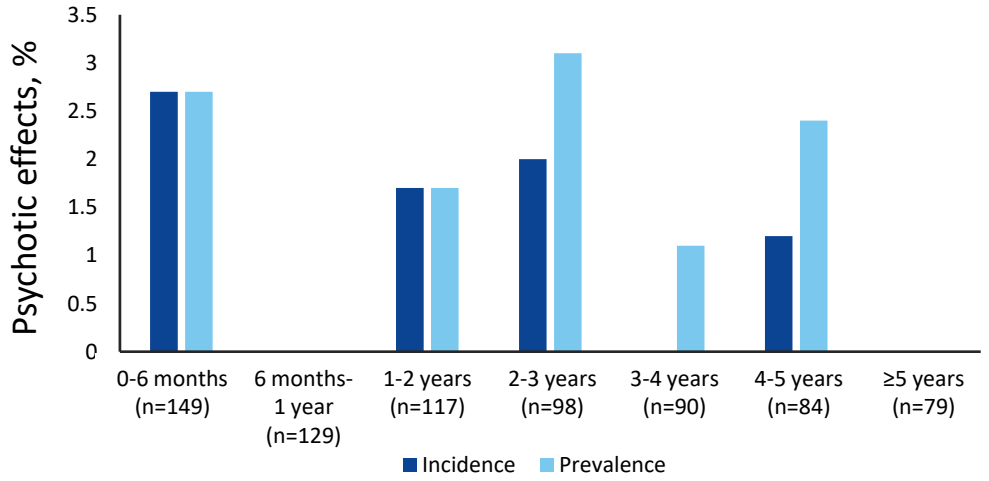
1. Solomon BJ, et al. *J Clin Oncol*. 2024:JCO2400581.

Incidence and Prevalence of CNS AEs did not Increase Over Time

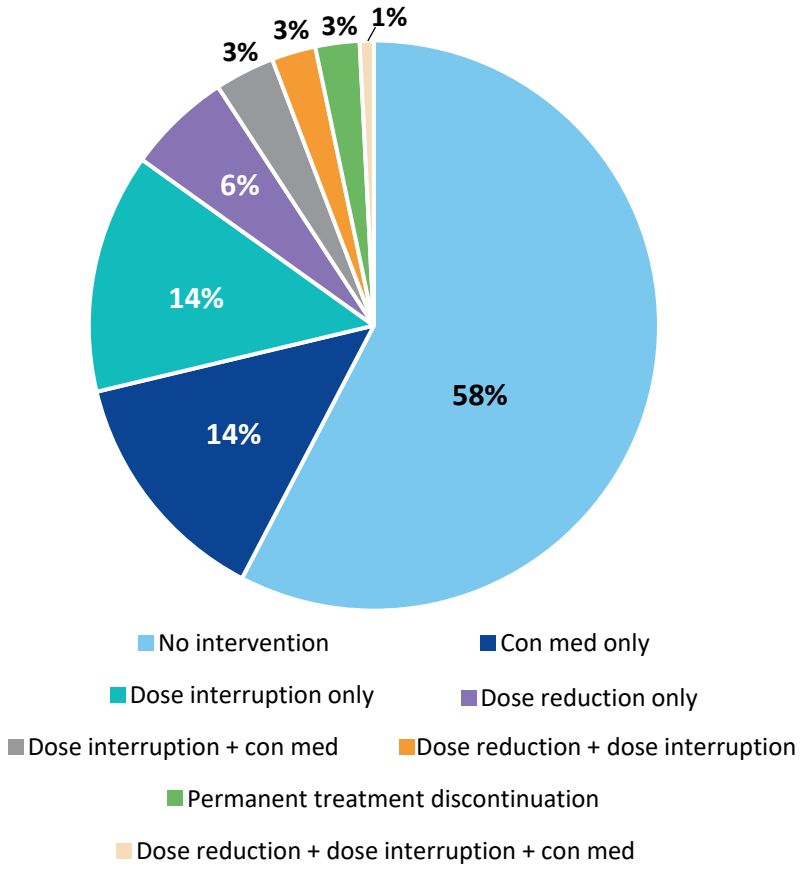


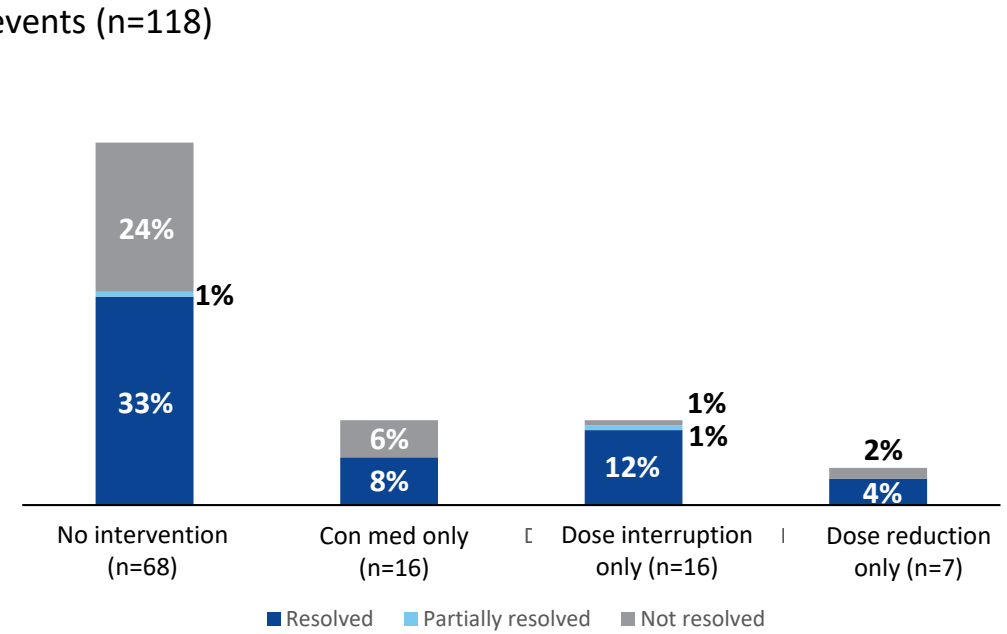






Most CNS AEs did not Require Pharmacological Intervention





- More than half of the CNS AEs did not require any pharmacological intervention; management strategies to minimize the impact of CNS effects are useful[1]
- Overall, 60% of CNS AEs resolved, either with management strategies, or dose interruption, or concurrent medication
- Permanent treatment discontinuation due to CNS AEs occurred in 3% of patients

con, concurrent; med, medication.

1. Liu G, et al. *Lung Cancer*. 2024;191:107535.

Conclusion

- This post hoc analysis suggests that with long exposure to lorlatinib, no new safety signals emerged, and treatment discontinuation remained low after 5 years of follow-up
- Most AEs occurred within 4 months of starting treatment; grade ≥3 events occurred within 9 months and few patients permanently discontinued lorlatinib due to AEs
- Hyperlipidemia events occurred shortly after the start of treatment, and were primarily managed with lipid-lowering agents
- Most weight gain events were managed with lifestyle modifications
- The incidence and prevalence of CNS AEs decreased over time; long-term analysis confirmed that CNS AEs remained manageable over time
- Most AEs resolved with dose modifications indicating that these strategies are effective to mitigate toxicity

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