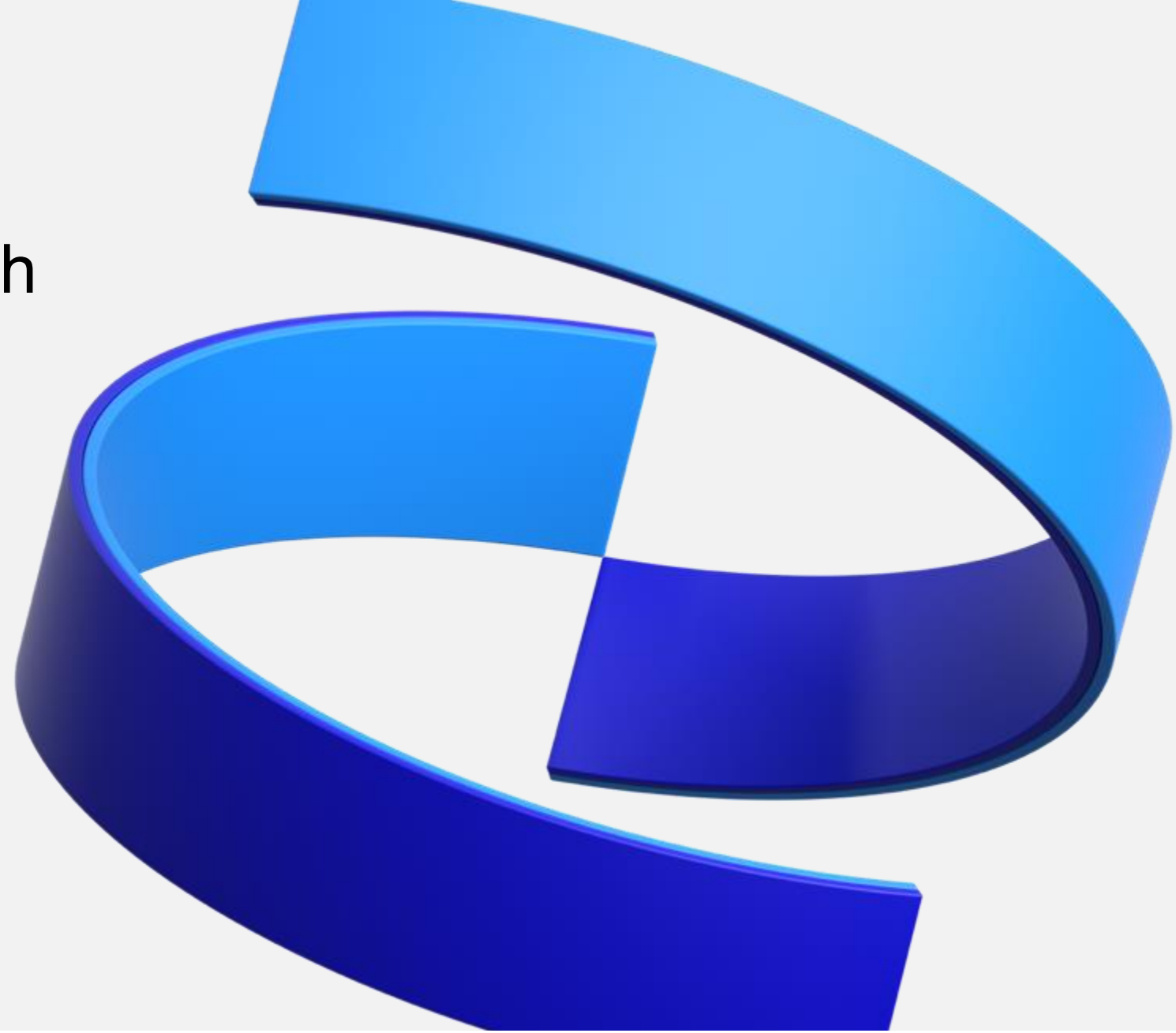
# Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase 3 CROWN Study



April 2025

EM-DEU-lor-0118

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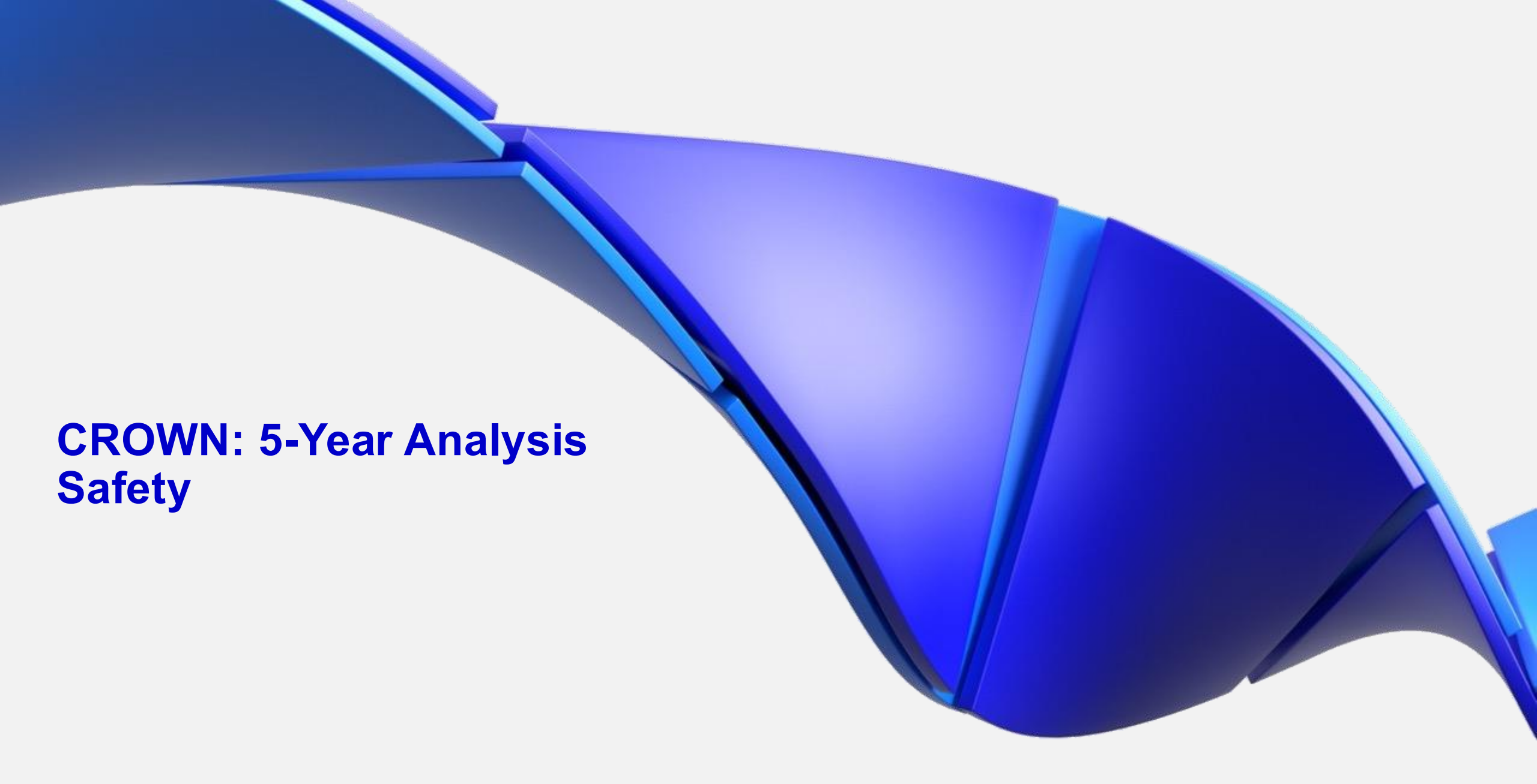
# CROWN: 5-Year Analysis
# Safety



# CROWN: Summary of Adverse Events (Safety Population)

- With longer follow-up, no new safety signals have emerged[1]

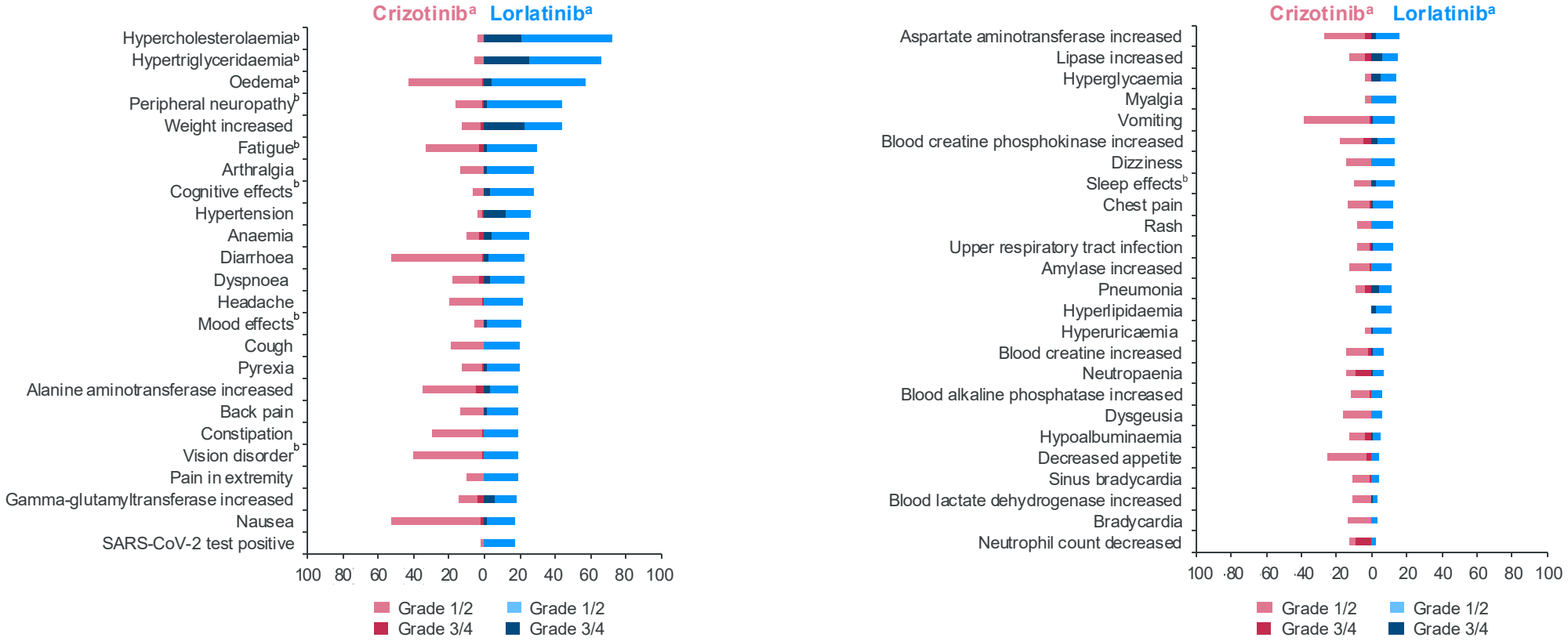
| Event, n (%) | Lorlatinib (n=149) | Crizotinib (n=142) |
|---|---|---|
| **All-causalities AEs** | | |
| Any-grade AE | 149 (100) | 140 (99) |
| Grade 3/4 AE | 115 (77) | 81 (57) |
| Death | 14 (9) | 7 (5) |
| Any serious AE | 65 (44) | 45 (32) |
| AEs leading to temporary discontinuations | 92 (62) | 68 (48) |
| AEs leading to dose reduction | 34 (23) | 21 (15) |
| AEs leading to permanent treatment discontinuation | 16 (11) | 15 (11) |
| **TRAEs** | | |
| Any-grade AE | 145 (97) | 133 (94) |
| Grade 3/4 AE | 99 (66) | 55 (39) |
| Death | 2 (1) | 0 |
| Any serious AE | 14 (9) | 9 (6) |
| AEs leading to temporary discontinuations | 58 (39) | 51 (36) |
| AEs leading to dose reduction | 31 (21) | 19 (13) |
| AEs leading to permanent treatment discontinuation | 8 (5) | 8 (6) |

**AEs with lorlatinib are largely manageable with concomitant therapies, temporary treatment interruptions, and/or dose reductions[1,2]**

Data cutoff: October 31, 2023.
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.
Median duration of treatment: lorlatinib, 57.0 months; crizotinib, 9.6 months.
AE, adverse event; TRAE, treatment-related adverse event.

1. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 2. Solomon BJ, et al. *Lancet Respir Med*. 2023;11(4):354–366.

# CROWN: All-Causalities AEs Occurring in ≥10% of Patients in Any Treatment Group[1]
## (Safety Population)




**The most common grade 3 and 4 adverse events in the lorlatinib-treated group were hypertriglyceridaemia (24.8%), increased weight (22.8%), hypercholesterolaemia (21.5%), and hypertension (12.1%)[1,2]**

A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.

[a]For each event listed, the combined percentage shown represents the frequency of any grade AE. [b]This category comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes.

AE, adverse event.

1. Solomon BJ, et al. *J Clin Oncol*. 2024. Supplementary Appendix. doi:10.1200/JCO.24.00581. 2. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

# CROWN: Summary of CNS AEs in the Lorlatinib Group[1] (Safety Population)

| Cluster Term | Lorlatinib (n = 149) | | | | |
|---|---|---|---|---|---|
| | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| **Any AEs, n (%)** | 63 (42) | 36 (24) | 18 (12) | 8 (5) | 1 (1) |
| Cognitive effects[a] | 41 (28) | 25 (17) | 11 (7) | 5 (3) | 0 |
| Mood effects[b] | 31 (21) | 17 (11) | 12 (8) | 2 (1) | 0 |
| Speech effects[c] | 9 (6) | 6 (4) | 2 (1) | 1 (1) | 0 |
| Psychotic effects[d] | 8 (5) | 5 (3) | 1 (1) | 1 (1) | 1 (1) |

The frequency and severity of CNS AEs were in line with prior analyses[2,3]

Data cutoff: October 31, 2023.
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.
[a]Cognitive effects were any event from cognitive and attention disorders and disturbances, deliria (including confusion), or mental impairment disorders.
[b]Mood effects were any event from anxiety disorders and symptoms, depressed mood disorders and disturbances, manic and bipolar mood disorders and disturbances, mood disorders and disturbances not elsewhere classified, or personality disorders and disturbances in behavior.
[c]Speech effects were any event from speech and language abnormalities.
[d]Psychotic effects were any event from SMQ narrow psychosis and psychotic disorders or PT of psychotic symptom.
AE, adverse event; CNS, central nervous system; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, Standardized MedDRA Query.
1. Solomon BJ, et al. *J Clin Oncol*. 2024. Supplementary Appendix. doi:10.1200/JCO.24.00581. 2. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 3. Solomon BJ, et al. *Lancet Respir Med*. 2023;11(4):354–366.

# CROWN: Summary of Cardiovascular Adverse Reactions[1] (Safety Population)

| | Lorlatinib (n=149), n (%) | | | | | Crizotinib (n=142), n(%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any Grade[a] | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| With any CV adverse events | 42 (28) | 19 (13) | 8 (5) | 10 (7) | 1 (1) | 40 (28) | 15 (11) | 13 (9) | 11 (8) | 1 (1) |
| SMQ ischaemic heart disease | 21 (14) | 14 (9) | 1 (1) | 6 (4) | 0 | 25 (18) | 15 (11) | 3 (2) | 6 (4) | 1 (1) |
| SMQ embolic and thrombotic events | 13 (9) | 4 (3) | 4 (3) | 4 (3) | 0 | 16 (11) | 3 (2) | 8 (6) | 5 (4) | 0 |
| Cluster cardiac failure | 7 (5) | 1 (1) | 2 (1) | 2 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| SMQ haemorrhagic central nervous system vascular conditions | 4 (3) | 0 | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 1 (1) | 0 | 0 |
| SMQ ischaemic central nervous system vascular conditions | 5 (3) | 0 | 1 (1) | 4 (3) | 0 | 2 (1) | 0 | 0 | 2 (1) | 0 |

The frequency of cardiovascular adverse reactions was similar between patients treated with lorlatinib and those treated with crizotinib[2]

**With longer follow-up and longer exposure to lorlatinib, cardiovascular AEs did not increase in frequency or severity[2,3]**

Data cutoff: October 31, 2023.
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.
Median duration of treatment: lorlatinib, 57.0 months; crizotinib, 9.6 months.
[a]Four patients in the lorlatinib group died due to pulmonary embolism, cardiac failure, cardiac failure acute, and basal ganglia hemorrhage (n=1 each).
Cardiovascular events were cardiac death, sudden cardiac death, sudden death, and from SMQ embolic and thrombotic events, cluster cardiac failure, SMQ ischaemic heart disease, SMQ hemorrhagic CNS vascular conditions, and SMQ ischemic CNS vascular conditions. Cluster cardiac failure included the preferred terms: cardiac failure, ejection fraction decreased, pulmonary oedema, acute left ventricular failure, acute right ventricular failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiac failure high output, cardiopulmonary failure, chronic left ventricular failure, chronic right ventricular failure, left ventricular failure, right ventricular failure, and ventricular failure.
AE, adverse event; CV, cardiovascular; SMQ, Standardized MedDRA Query.
1. Solomon BJ, et al. *J Clin Oncol*. 2024. Supplementary Appendix. doi:10.1200/JCO.24.00581. 2. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 3. Solomon BJ, et al. *Lancet Respir Med*. 2023;11(4):354–366.

# CROWN: CROWN: Summary of Cardiovascular AEs in Patients Who Had Hyperlipidaemia at Baseline and/or Developed Hyperlipidaemia During the Study[1]

| | Lorlatinib (n=134), n (%) | | | | | Crizotinib (n=32), n (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any Grade[a] | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| With any CV AEs | 37 (28) | 18 (13) | 7 (5) | 8 (6) | 1 (1) | 15 (47) | 8 (25) | 4 (13) | 3 (9) | 0 |
| SMQ ischemic heart disease | 21 (16) | 14 (10) | 1 (1) | 6 (4) | 0 | 10 (31) | 7 (22) | 2 (6) | 1 (3) | 0 |
| SMQ embolic and thrombotic events | 10 (7) | 3 (2) | 3 (2) | 4 (3) | 0 | 6 (19) | 2 (6) | 2 (6) | 2 (6) | 0 |
| Cluster cardiac failure | 6 (4) | 1 (1) | 2 (1) | 1 (1) | 0 | 0 | 0 | 0 | 0 | 0 |
| SMQ hemorrhagic central nervous system vascular conditions | 4 (3) | 0 | 1 (1) | 1 (1) | 1 (1) | 0 | 0 | 0 | 0 | 0 |
| SMQ ischemic central nervous system vascular conditions | 4 (3) | 0 | 1 (1) | 3 (2) | 0 | 1 (3) | 0 | 0 | 1 (3) | 0 |

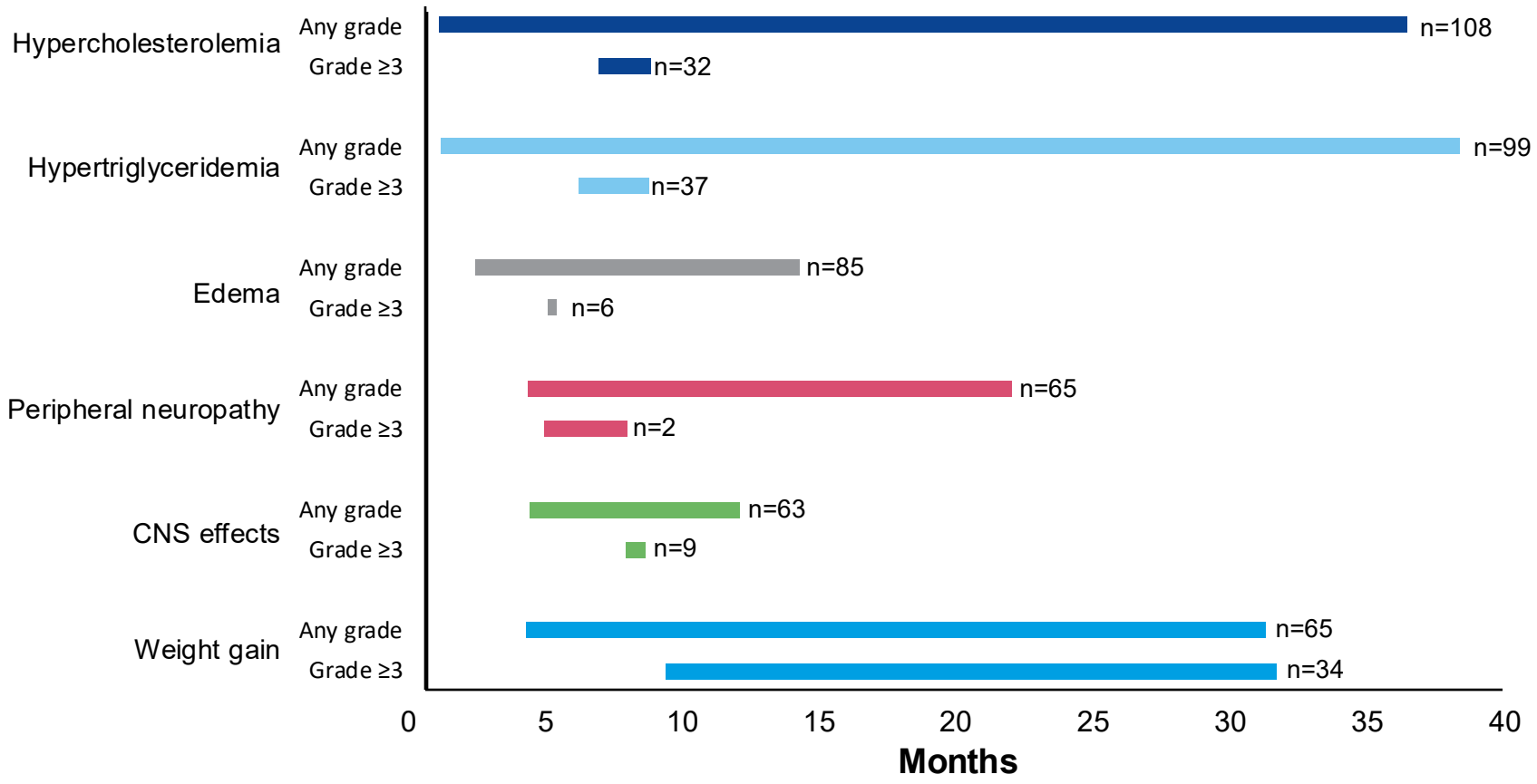
**Although a higher number of patients in the lorlatinib group had hyperlipidaemia, the incidence of cardiovascular AEs was lower with lorlatinib than with crizotinib, mostly due to fewer occurrences of ischemic heart disease and embolic and thrombotic events[2]**

Data cutoff: October 31, 2023.
Median duration of treatment: lorlatinib, 57.0 months; crizotinib, 9.6 months.
[a]Three patients in the lorlatinib group died due to cardiac failure, cardiac failure acute, and basal ganglia hemorrhage (n=1 each).
Cardiovascular events were cardiac death, sudden cardiac death, sudden death, and from SMQ embolic and thrombotic events, cluster cardiac failure, SMQ ischemic heart disease, SMQ hemorrhagic CNS vascular conditions, and SMQ ischemic CNS vascular conditions. Cluster cardiac failure included the preferred terms: cardiac failure, ejection fraction decreased, pulmonary edema, acute left ventricular failure, acute right ventricular failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiac failure high output, cardiopulmonary failure, chronic left ventricular failure, chronic right ventricular failure, left ventricular failure, right ventricular failure, and ventricular failure.
AE, adverse event; CV, cardiovascular; SMQ, Standardized MedDRA Query.
1. Solomon BJ, et al. *J Clin Oncol*. 2024. Supplementary Appendix. doi:10.1200/JCO.24.00581. 2. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

# CROWN: Expanded Safety (WCLC 2024)

# Median Time to Onset and Median Duration of AEs

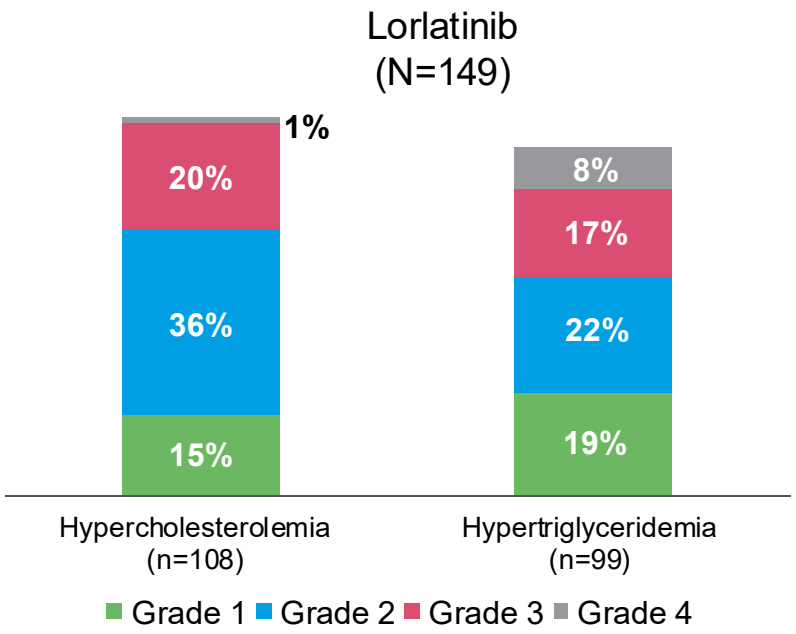
- Hyperlipidemia:
  - Time to onset, any-Grade: 15 days
  - Duration, any-Grade: ≈37 months
  - Time to onset, Grade ≥3: ≈6 months
- Edema, peripheral neuropathy, and CNS effects:
  - Time to onset, any-Grade: 2–4 months
  - Duration, any-Grade: 8–18 months
- Only weight gain showed grade ≥3 AE that lasted more than 3 months

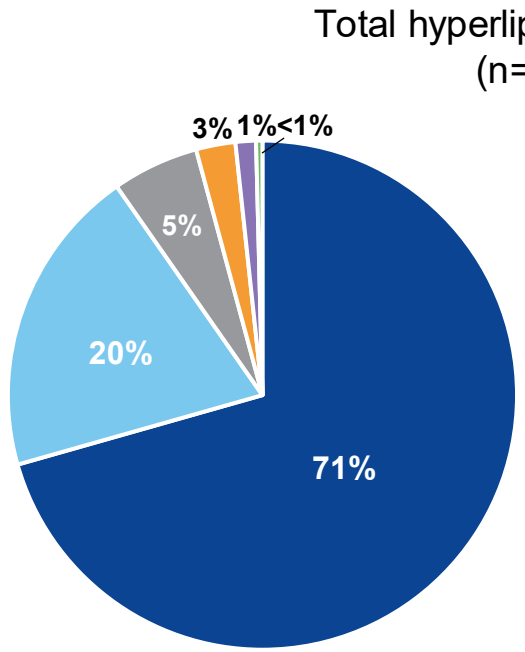


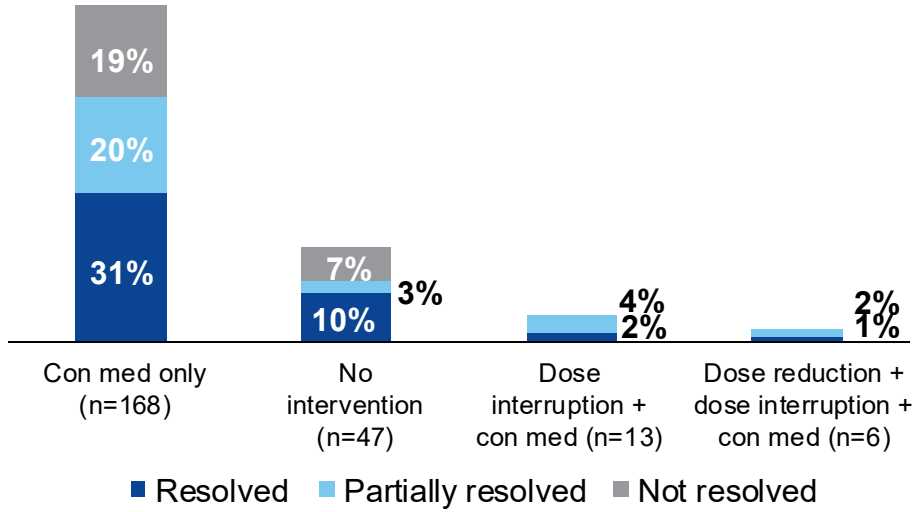

AE, adverse event; CNS, central nervous system.

Bauer TM, et al. Presented at: WCLC Annual Meeting; September 7-10th, 2024 San Diego, CA.

# Most Hyperlipidemia Events were Managed Medically



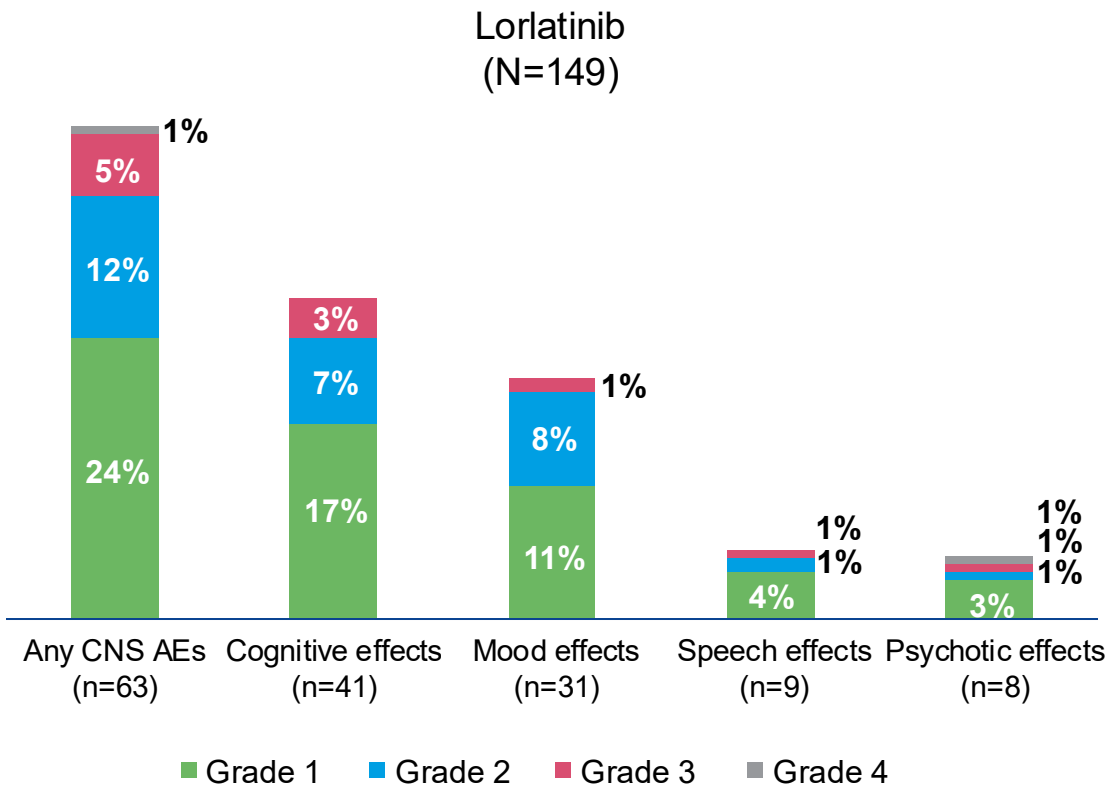

- Hypercholesterolemia and hypertriglyceridemia were observed in the majority of patients treated with lorlatinib

- Most of the hyperlipidemia events were managed and controlled with lipid-lowering agents[1]
- Pitavastatin, pravastatin, or rosuvastatin should initially be considered based on their low involvement with CYP3A4[2]
- 45% of hyperlipidemia events resolved
- 1 event led to permanent treatment discontinuation

con, concurrent; CYP, cytochrome P450; med, medication.

1. Liu G, et al. *Lung Cancer*. 2024;191:107535. 2. Neuvonen PJ, et al. *Clin Pharmacol Ther.* 2006;80:565–581.
Bauer TM, et al. Presented at: WCLC Annual Meeting; September 7-10th, 2024; San Diego, CA.

# Most CNS AEs Were of Grade 1/2 Severity

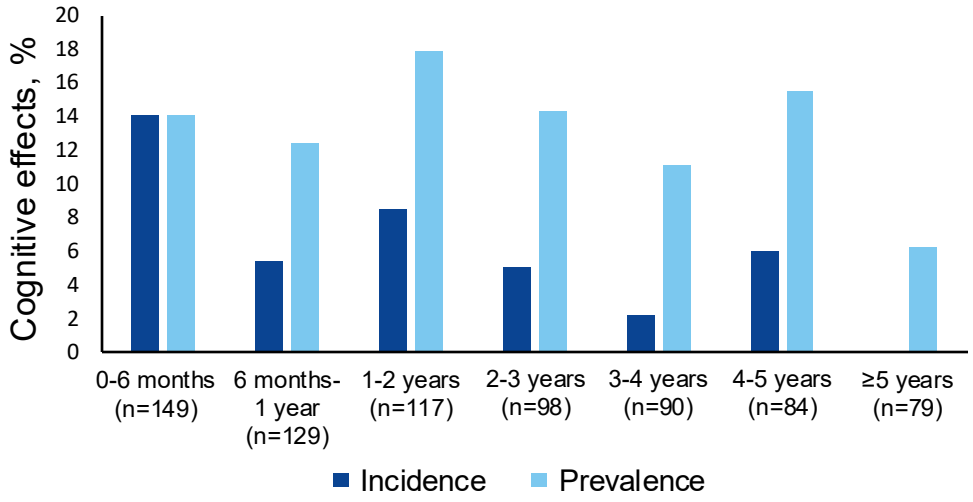


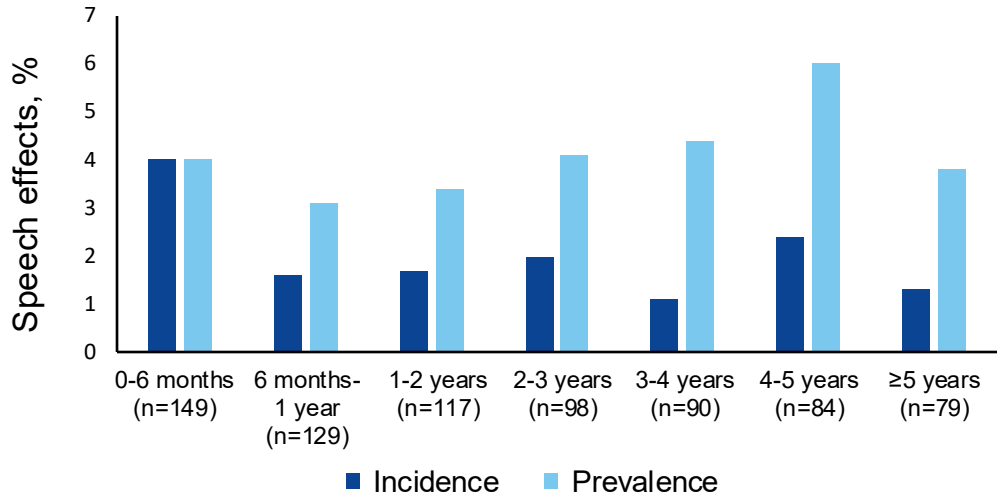

- All-causality CNS AEs occurred in 42% of patients, the majority of which (86%) were of grade 1/2 severity[1]
- As previously reported, CNS AEs occurred in 67% of patients who had prior brain radiotherapy (n=9) and 41% of patients without prior brain radiotherapy (n=140)[1]

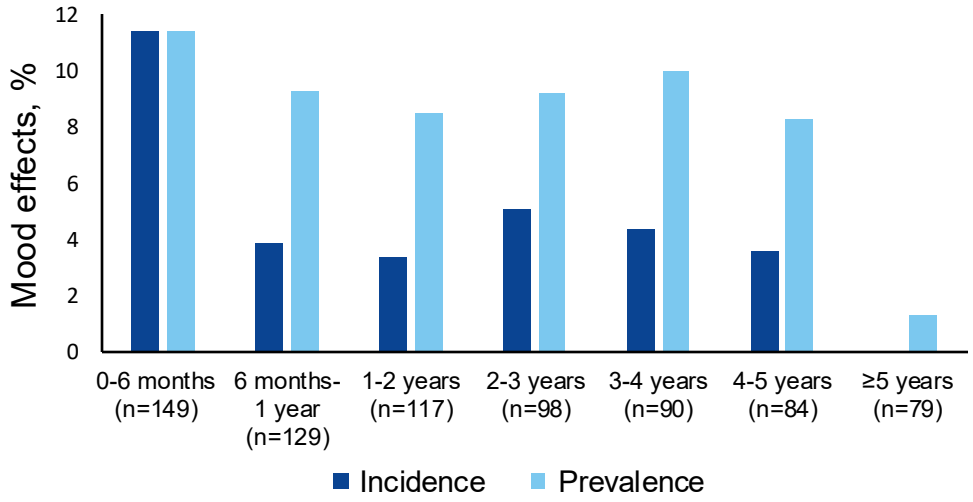
AE, adverse event; CNS, central nervous system.

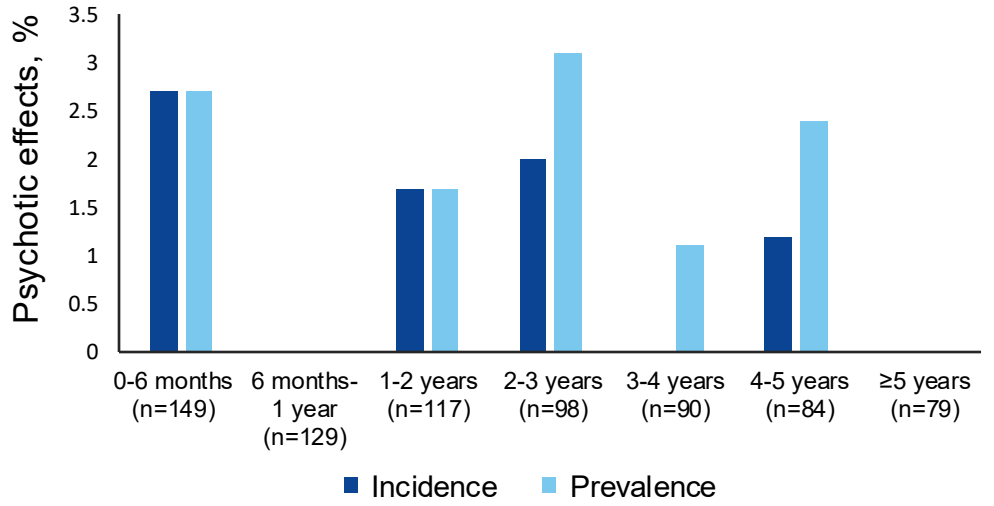
1. Solomon BJ, et al. *J Clin Oncol*. 2024 May 31:JCO2400581.
Bauer TM, et al. Presented at: WCLC Annual Meeting; September 7-10th, 2024.

# Incidence and Prevalence of CNS AEs did not Increase Over Time

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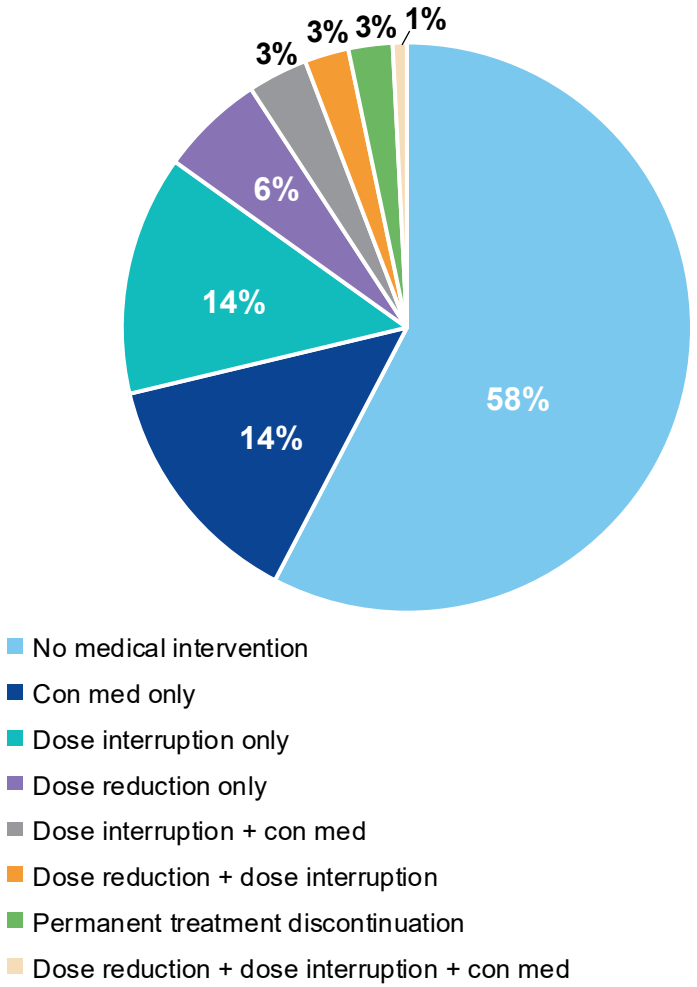
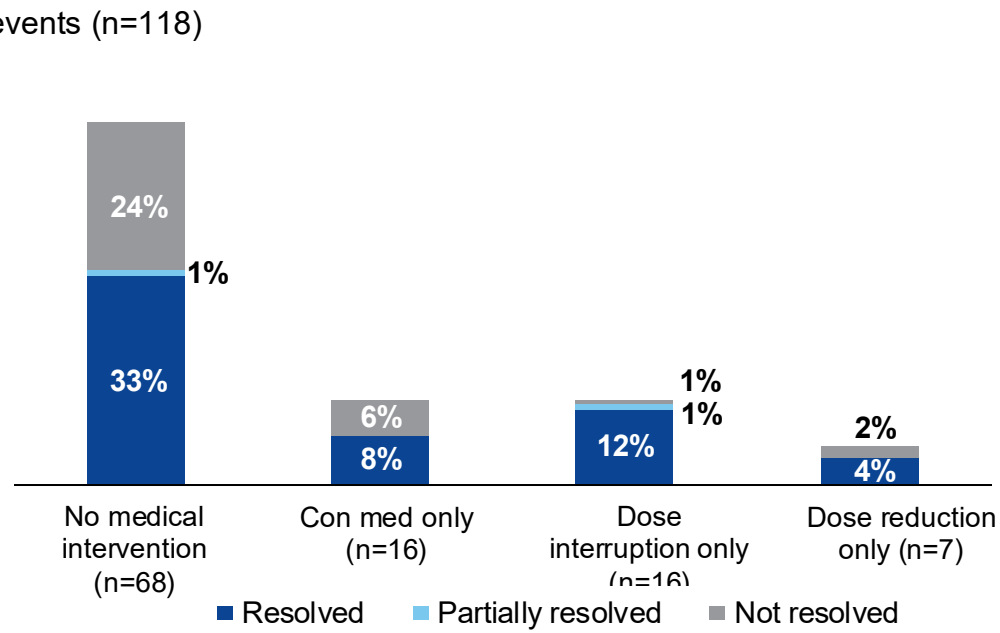
# Most CNS AEs did not Require Medical Intervention



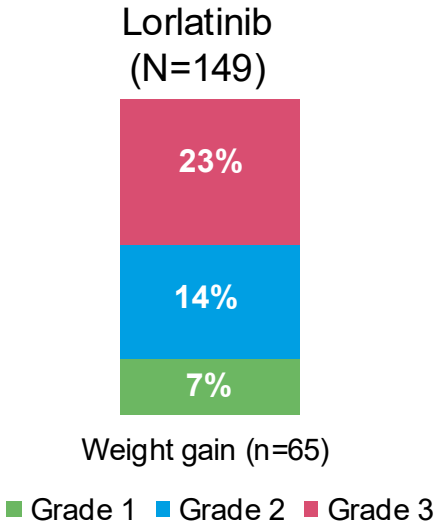




- More than half of the CNS AEs did not require any pharmacological intervention; management strategies to minimize the impact of CNS effects are useful[1]
- 60% of CNS AEs resolved, either with management strategies, dose interruption, or concurrent medication
- 3% of events led to permanent treatment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

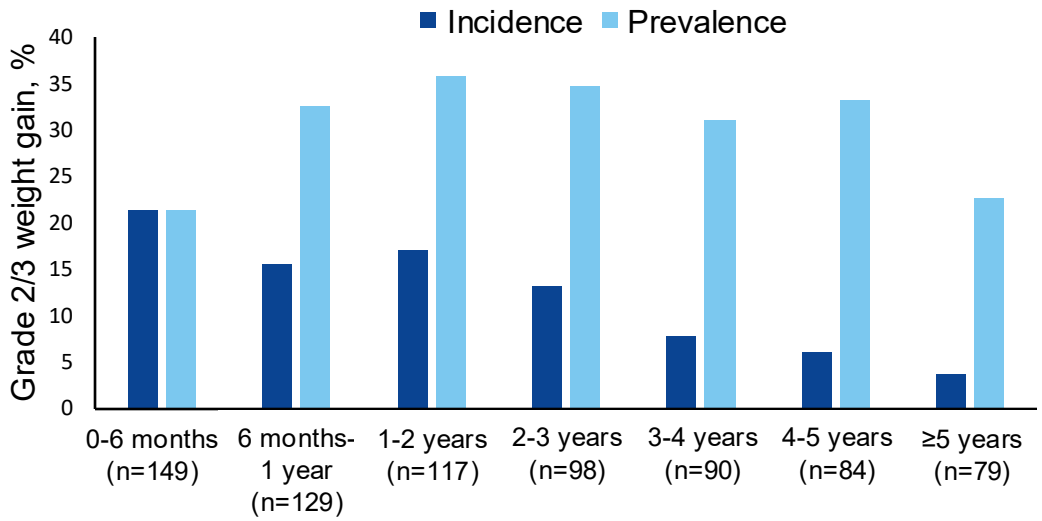
AE, adverse effect; CNS, central nervous system; con, concurrent; med, medication.

1. Liu G, et al. *Lung Cancer*. 2024;191:107535.
Bauer TM, et al. Presented at: WCLC Annual Meeting; September 7-10th, 2024; San Diego, CA.

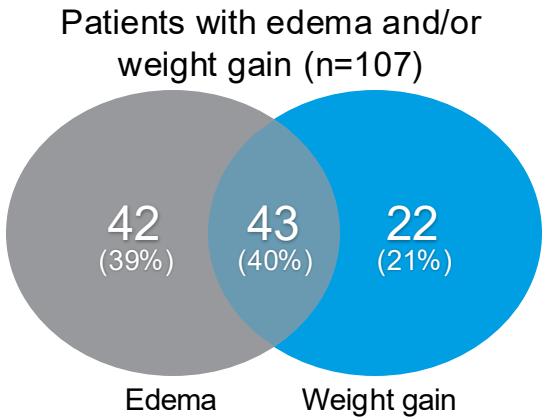
# Weight Gain Occurred in 44% of Patients




| | 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) |

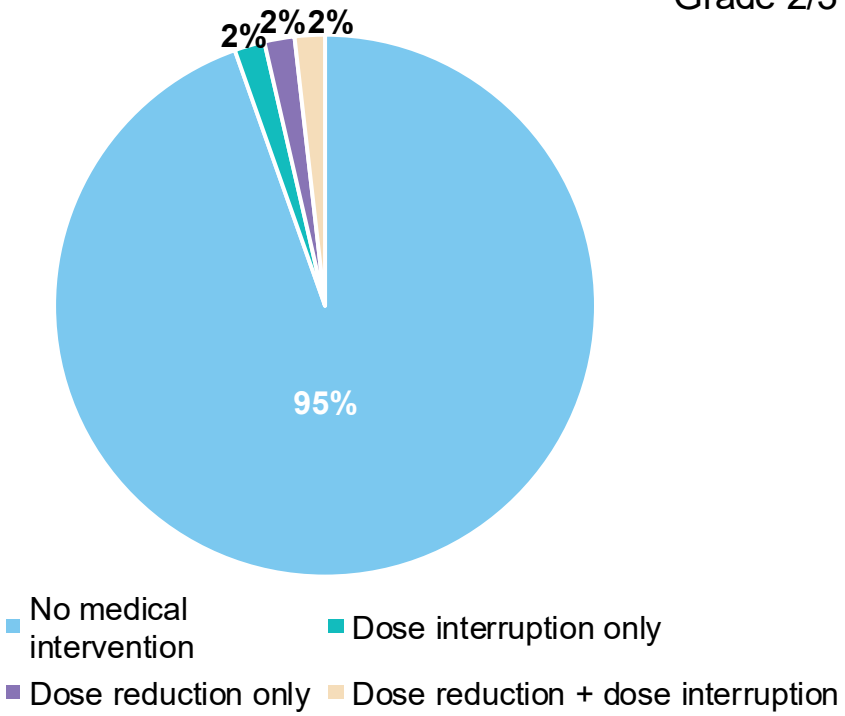


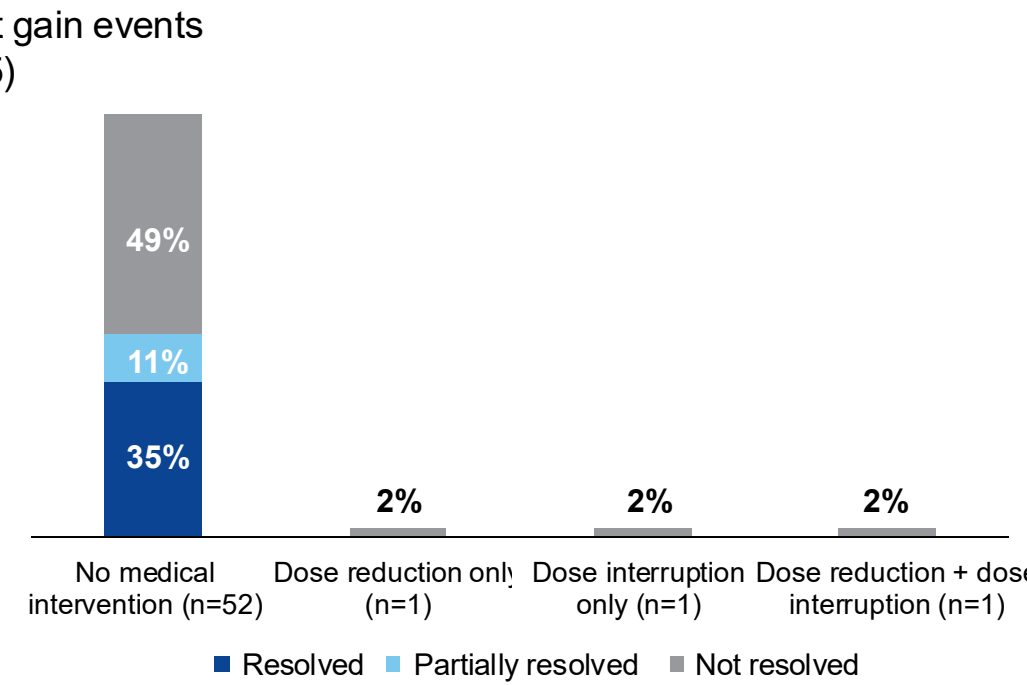

- Baseline body weight did not influence subsequent weight gain
- Incidence and prevalence of weight gain did not increase over time
- Weight gain and edema seem to correlate only in a fraction of patients, suggesting different pathogenic mechanisms




AE, adverse event.
Bauer TM, et al. Presented at: WCLC Annual Meeting; September 7-10th, 2024; San Diego, CA.

# Most Weight Gain Events Were Managed With Lifestyle Modifications




- Weight gain was primarily managed with lifestyle modifications[1]
- 35% of all weight gain events resolved with no medical intervention

1. Liu G, et al. *Lung Cancer*. 2024;191:107535.
Bauer TM, et al. Presented at: WCLC Annual Meeting; September 7-10th, 2024; San Diego, CA.