

Identifying and Mitigating Adverse Events Associated With ALK Inhibitors for Advanced ALK-Positive Non-Small-Cell Lung Cancer

- In advanced NSCLC, ALK may be rearranged in ~5% of cases¹⁻³
- Advanced ALK-positive NSCLC can be treated with several approved ALK TKIs
- National guidelines currently list the following as preferred treatment options for **first-line therapy** for patients with advanced ALK-positive NSCLC: alectinib, brigatinib, ensartinib, and lorlatinib; ceritinib and crizotinib may also be useful in specific circumstances with limited access to preferred agents³

ALK Inhibitors: Checklist of Key AEs⁴⁻⁹

- ALK inhibitors are generally well tolerated
- Side effect profiles differ among ALK inhibitors

Drug	Frequent AEs (Incidence in Clinical Trials)			Key Lab Abnormalities (Grade 3/4 Incidence in Clinical Trials)
Alectinib*	☐ Hepatotoxicity (41%) ☐ Constipation (39%) ☐ Fatigue (36%)	☐ Myalgia (31%) ☐ Edema (29%)	☐ Rash (23%) ☐ Cough (21%)	☐ Increased CPK (6%)
Brigatinib††	☐ Diarrhea (53%) ☐ Fatigue (32%) ☐ Nausea (30%) ☐ Rash (40%)	☐ Cough (35%) ☐ Myalgia (28%) ☐ Headache (22%)	☐ Hypertension (NA) ☐ Vomiting (21%) ☐ Dyspnea (25%)	☐ Increased CPK (24%)
Ensartinib* [§]	☐ Rash (66%) ☐ Musculoskeletal pain (36%) ☐ Constipation (31%)	☐ Pruritus (30%) ☐ Cough (31%) ☐ Nausea (28%)	☐ Edema (27%) ☐ Fatigue (21%) ☐ Pyrexia (22%)	☐ Increased urate (39%)
Lorlatinib*	☐ Edema (56%) ☐ Peripheral neuropathy (44%) ☐ Weight gain (31%) ☐ Cognitive effects (28%)	☐ Fatigue (27%) ☐ Dyspnea (27%) ☐ Arthralgia (24%)	☐ Diarrhea (23%) ☐ Mood effects (21%) ☐ Cough (21%)	☐ Hypercholesterolemia (21%) ☐ Hypertriglyceridemia (21%)
Ceritinib†**	☐ Diarrhea (85%) ☐ Nausea (69%) ☐ Vomiting (67%)	☐ Abdominal pain (40%) ☐ Fatigue (45%)	☐ Decreased appetite (34%) ☐ Cough (25%)	☐ Increased GGT (49%) ☐ Increased ALT (34%)
Crizotinib†	☐ Vision disorders (71%) ☐ Diarrhea (61%) ☐ Vomiting (46%)	☐ Edema (49%) ☐ Constipation (43%) ☐ Abdominal pain (26%)	☐ URI (32%) ☐ Dysgeusia (26%)	☐ Increased ALT (15%) ☐ Neutropenia (11%) ☐ Hypophosphatemia (10%)

*AEs in ≥20% of patients. †AEs in ≥25% of patients. ‡Pooled data unavailable; rates from ALTA 1L study (N = 273). §Pooled data unavailable; rates from eXALT3 study (N = 289).

**Pooled data unavailable; rates from ASCEND-4 study (N = 189). ††Pooled data unavailable; rates from PROFILE 1014 study (N = 171).

Managing Key AEs With Preferred ALK Inhibitors⁴⁻⁹

- Dose reductions or interruptions may be appropriate in certain instances; the following are recommendations for specific AEs as listed in the prescribing information

Drug	ILD/Pneumonitis	CPK Elevation	Visual Disturbance	Bradycardia	Hepatotoxicity	Hemolytic Anemia	Hypertension
Alectinib	• Permanently discontinue for treatment-related event	• >5x ULN: hold until BL recovery/≤2.5x ULN, resume at same dose • >10x ULN or second occurrence of >5x ULN: hold until BL recovery/≤2.5x ULN, resume at lower dose	• No specific guidance in PI	• Permanently discontinue if no contributing concomitant medication; if identified/discontinued, resume at reduced dose after asymptomatic	• If ALT/AST elevation >5x ULN with bili ≤2x ULN, hold until BL recovery/≤3x ULN, resume at reduced dose • If ALT/AST elevation >3x ULN with bili >2x ULN (and no cholestasis or hemolysis), permanently discontinue • If bili >3x ULN, hold until BL recovery/≤1.5x ULN, resume at reduced dose	• If suspected, hold • If confirmed, permanently discontinue or consider resuming at a reduced dose after resolution	• No specific guidance in PI
Brigatinib	• Monitor for new or worsening respiratory symptoms, particularly during the first week of treatment • Grade 1: hold until BL recovery; resume at same dose • Grade 2: hold until BL recovery; resume at lower dose • Grade 3/4/recurrence of lower grade: permanently discontinue	• Grade 3/4 (>5x ULN) with grade ≥2 muscle pain/ weakness: hold until ≤2.5x ULN, resume at same dose	• Grade 2/3: hold until grade ≤1, then resume at lower dose • Grade 4: permanently discontinue	• If symptomatic, hold until recovery to asymptomatic • If life threatening, permanently discontinue • Review concomitant medication to determine if contributing	• If ALT/AST elevation >5x ULN with bili ≤2x ULN, hold until ≤3x ULN, resume at reduced dose • If ALT/AST elevation >3x ULN with bili >2x ULN (and no cholestasis or hemolysis), permanently discontinue	• No specific guidance in PI	• Monitor blood pressure after 2 weeks and then at least monthly during treatment • Grade 3: hold until ≤ grade 1, then resume at same dose • Grade 4: hold until ≤ grade 1, then resume at lower dose or permanently discontinue
Ensartinib	• Permanently discontinue for any event	• >5x ULN: hold until BL recovery/≤2.5x ULN, resume at same dose • >10x ULN or second occurrence of >5x ULN: hold until BL recovery/≤2.5x ULN, resume at lower dose	• Grade 2/3: hold until grade ≤1, then resume at lower dose • Grade 4: permanently discontinue	• Permanently discontinue if no contributing concomitant medication; if identified/discontinued, resume at reduced dose after asymptomatic	• If ALT/AST elevation >5x ULN with bili ≤2x ULN, hold until ≤3x ULN, resume at reduced dose • If ALT/AST elevation >3x ULN with bili >2x ULN (and no cholestasis or hemolysis), permanently discontinue	• No specific guidance in PI	• No specific guidance in PI
Lorlatinib	• Permanently discontinue for treatment-related event	• No specific guidance in PI	• Grade 3: hold until grade ≤1; resume at same dose • Grade 4: hold until grade ≤1; resume at lower dose/ discontinue	• No specific guidance in PI	• No specific guidance in PI	• No specific guidance in PI	• Monitor blood pressure after 2 weeks and then at least monthly during treatment • Grade 3: hold until ≤ grade 1, then resume at same dose • Grade 4: hold until ≤ grade 1, then resume at lower dose or permanently discontinue

- The safety profile of lorlatinib is distinct from other ALK inhibitors¹⁰

Lorlatinib ^{4,10}		
AE	Notes	Management
Hyperlipidemia	• Serum cholesterol and triglyceride increases can occur (grade 3 and 4, 21% for each in clinical trials) • 83% required lipid-lowering medications	• Serum cholesterol and triglyceride should be monitored before starting lorlatinib, then at 1 and 2 mo and periodically • Lipid-lowering agents should be initiated/increased if hyperlipidemia occurs (ie, pitavastatin, pravastatin, or rosuvastatin) • If grade 4 hyperlipidemia, hold lorlatinib until recovery to grade ≤2, then resume at same dose; if recurrence of severe hyperlipidemia, resume at reduced dose
CNS effects	• Seizures, psychotic effects and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep can occur (CNS effects in 52% in clinical trials) • 2.1% required treatment discontinuation	• If grade 1 AE, continue or hold until recovery to BL; resume at same or reduced dose • If grade 2/3 AE, hold until grade 0 or 1; resume at reduced dose • If grade 4 AE, permanently discontinue • Consider cognitive behavioral therapy and other strategies to minimize effects
Edema	• Can occur in more than one half of patients	• Management can include elevation of lower extremities, compression, exercise, limiting salt, massage; limited study of use of diuretics

First dose reduction for AE: 75 mg PO QD; second dose reduction: 50 mg PO QD.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bili, bilirubin; BL, baseline; CNS, central nervous system; CPK, creatine phosphokinase; ILD, interstitial lung disease; NA, not available; NSCLC, non-small-cell lung cancer; PI, prescribing information; ULN, upper limit of normal; URI, upper respiratory infection.

References

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