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Understanding Safety Profiles of ROS1 TKIs in Advanced Non-Small Cell Lung Cancer

Ryan Quigley:
Welcome to *AudioAbstracts* on ReachMD. I'm Ryan Quigley, and today I'll be discussing a systematic review and proportional meta-analysis examining the toxicity profiles of ROS1 tyrosine kinase inhibitors in advanced non-small cell lung cancer.

Targeted therapies have significantly improved outcomes for patients with ROS1-rearranged non-small cell lung cancer. Many patients remain on these therapies long-term, so considering safety and tolerability is as important as efficacy in clinical decision-making. However, most of the available safety data on these therapies are from individual clinical trials, making it difficult to compare adverse event risks across agents in day-to-day practice.

To address this gap, researchers conducted the first comprehensive synthesis of toxicity data across ROS1 tyrosine kinase inhibitors to characterize both overall and drug-specific adverse event patterns. Their systematic review with proportional meta-analysis was published in *Frontiers in Pharmacology* in 2025. The authors included 26 phase two and phase three trials representing more than 5,200 patients which evaluated seven ROS1 inhibitors.

The primary outcomes assessed the incidence of all-grade adverse events and serious adverse events. Secondary outcomes focused on specific toxicity patterns, such as neurological, gastrointestinal, hepatic, and hematologic effects.

Here's what they found.

Across all agents, all-grade adverse events were nearly universal. Between 90 and 99 percent of patients experienced at least one adverse event, regardless of which ROS1 inhibitor was used.

Serious adverse events, however, varied more meaningfully by drug. Repotrectinib had the lowest pooled rate of serious adverse events, at about 29 percent, while unecritinib had the highest rate, approaching 47 percent.

The analysis also revealed distinct toxicity signatures for individual agents.

Repotrectinib was associated with a high rate of dizziness, whereas entrectinib showed higher rates of fatigue, and lorlatinib was linked to more frequent edema.

Elevated liver enzymes and higher rates of serious hepatic adverse events stood out with taletrectinib and unecritinib.

Gastrointestinal toxicities were also prominent, with some cases of diarrhea, nausea, or vomiting severe enough to require dose modification or discontinuation, particularly with ceritinib, taletrectinib, crizotinib, and unecritinib.

With all that being said, why does this matter?

For clinicians, these findings reinforce that ROS1 inhibitors are not interchangeable from a safety standpoint. Matching the toxicity profile of a drug to a patient's baseline risks, such as liver disease, neurologic symptoms, or frailty, may help optimize long-term treatment success.

The authors also highlight several limitations. This wasn't a head-to-head comparison and causality can't be established. In terms of the quality of data available, many newer agents were represented by only one or two studies and most trials excluded older adults and patients with significant organ dysfunction, limiting generalizability.

Still, this work provides the most comprehensive overview to date of ROS1 inhibitor toxicities to support individualized treatment

decisions, proactive monitoring, and enriched counseling in this patient population.

This has been an *AudioAbstract*, and I'm Ryan Quigley. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

Reference:

Jiang BX, Zeng JW, Yan JJ, Zhao LY. Toxicity profiles of ROS1 tyrosine kinase inhibitors in advanced non-small cell lung cancer: a systematic review and proportional meta-analysis. *Front Pharmacol*. 2025;16:1644034. Published 2025 Aug 29. doi:10.3389/fphar.2025.1644034