Effects of semaglutide on the exposure of alectinib in patients with NSCLC

Background: Alectinib serves as a preferred first-line treatment for advanced anaplastic lymphoma kinaseepositive (ALK+) non-small cell lung cancer (NSCLC), offering durable efficacy. Nonetheless, its side effect of substantial weight gain poses serious health risks for patients.

Semaglutide, a highly effective glucagon-like peptide 1 receptor agonist (GLP-1RA) for treating obesity, shows potential for mitigating alectinib-induced weight gain. However, its mechanism may also impact alectinib absorption, warranting investigation into a potential drug-drug interaction, given alectinib's exposure-response relationship (Groenland et al., Clin Pharmacol Ther 2021).

Methods: In this prospective crossover study, patients with ALK+ NSCLC receiving alectinib as standard of care, were sequentially treated with alectinib alone and alectinib combined with a single subcutaneous dose of semaglutide (2.0 mg) for both seven days. Plasma samples were collected for pharmacokinetic analysis after each week, while toxicity was also assessed. The primary endpoint was the alectinib exposure (area under the curve; AUC0-10h), with secondary endpoints including the minimum concentration (Ctrough), maximum concentration (Cmax), and toxicity.

Results: In 10 patients, co-administration of semaglutide significantly reduced alec tinib AUC0-10h by 32% (95% confidence interval (CI):-45% to-15%; p ¼ 0.004) compared to alectinib monotherapy. Semaglutide also decreased Ctrough and Cmax by 25% (95% CI:-46% to 3%; p ¼ 0.072) and 36% (95% CI:-48% to-20%; p ¼ 0.001) respectively, with fewer patients maintaining efficacy threshold levels (i.e. 435 ng/mL; 60% vs 100%). Additionally, combination therapy resulted in more overall toxicity (5 versus 25 events), predominantly grade 1 or 2 gastrointestinal side effects.

Conclusions: Our study reveals a clinically relevant and significant decrease in alectinib exposure with semaglutide co-administration, emphasizing the importance of caution due to a potential negative impact on alectinib effectiveness. Consequently, monitoring alectinib plasma concentrations in patients receiving semaglutide is crucial to ensure optimal exposure and treatment outcomes. Potentially, other GLP 1RAs may have a similar effect on alectinib exposure. Clinical trial identification: NL9702 (Dutch trial register)

Note from ALK Positive UK

1. This was a small trial and larger ones are needed.
2. Semaglutide is the active ingredient in Ozempic and Wegovy. Tirzepatide is the active ingredient in Mounjaro. Both drugs are GLP-1 receptor agonists. Therefore, it must not be assumed that Mounjaro would not also decrease the effectiveness of Alectinib.
3. We are not aware of any trials involving Brigatinib or Lorlatinib.

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