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LETTER TO THE JOURNAL

Semaglutide impairs bioavailability of alectinib: a note of warning based on a cross-over pharmacokinetic drug-drug interaction study

Alectinib is a first-line treatment for patients with advanced non-small cell lung cancer (NSCLC) harboring anaplastic lymphoma kinase-positive (*ALK*+) driver aberrations with a median progression-free survival of 35 months and a 5-year overall survival of 63% [1]. Currently, alectinib also shows improvement as an adjuvant treatment in resected stage IA-IIIB *ALK*+ NSCLC [2]. Alectinib has a mild safety profile, but a notable underreported side-effect is weight gain [3]. Studies show sarcopenic obesity rates doubling from 24% to 47% in the first year of treatment [3], with persisting weight gain appearing early [4]. Given patients' extended survival, this poses risks for metabolic, cardiovascular, and psychological health.

Interestingly, over the past few years, glucagon-like peptide 1 (GLP-1) receptor agonists semaglutide, liraglutide, and tirzepatide, have been approved as promising anti-obesity drugs [5]. Subcutaneous, once-weekly semaglutide induces a weight loss of 15% after 68 weeks [5]. Hence, semaglutide might pose an interesting means of treating alectinib-induced weight gain. Recently, it was reported that a patient who experienced 20 kg weight gain during treatment with alectinib and lorlatinib, achieved 5 kg weight loss in just 6 months with semaglutide [6].

In a retrospective analysis, alectinib plasma trough levels above 435 ng/mL correlated with prolonged effectiveness compared to lower exposures [7]. Despite moderate interpatient variability of 40%-45%, the lipophilicity of alectinib makes it highly dependent on dietary fat for sufficient dissolution and subsequent absorption in the gastro-intestinal tract to maintain adequate trough concentrations [7, 8]. Considering that semaglutide decreases appetite, patients may inadvertently decrease their dietary (fat) intake, hampering absorption of alectinib. Hence, we investigated the effects of semaglutide on the pharmacokinetics of alectinib to gain insight into the pharmacokinetic interplay between both.

Therefore, we included 10 patients in a two-period cross-over study comparing alectinib exposure on alectinib monotherapy (period A) versus co-administration of semaglutide (period B) (Supplementary Table S1). Each treatment period lasted one week. Semaglutide was administrated as a single dose of 2.0 mg subcutaneously. Further details on the methodology of this study and baseline patient characteristics are provided in the Supplementary Materials.

After alectinib monotherapy (period A), a geometric mean of the area under the curve ($AUC_{0\text{-}10h}$) of 7,114 ng × h/mL (coefficient of variation [CV] = 34%) was observed, compared to an $AUC_{0\text{-}10h}$ of 4,843 ng × h/mL (CV = 47%) after co-administering alectinib with subcutaneous semaglutide (period B). This change in alectinib geometric mean $AUC_{0\text{-}10h}$ constituted a significant and clinically relevant reduction of 32% (95% confidence interval [CI] = -45% to -15%; P = 0.004; Figure 1A and Supplementary Table S2) when co-administering semaglutide. Additionally, trough concentrations (C_{trough}) showed a similar trend towards lower concentrations with semaglutide, decreasing the geometric mean C_{trough} from 681 ng/mL (CV = 29%) to 509 ng/mL (CV = 66%), reflecting a relative difference of -25% (95% CI = -46% to 3%; P = 0.072) when alectinib was combined with semaglutide (period B) compared to alectinib alone (period A). The maximum concentration (C_{max}) decreased with 36% (95% CI = -48% to -20%; P = 0.001) with a C_{max} of alectinib of 875 ng/mL (CV = 31%) on monotherapy (period A) versus 563 ng/mL (CV = 42%) in the combination arm (period B).

Moreover, during alectinib monotherapy, all patients had C_{trough} levels surpassing the efficacy threshold (i.e. >435 ng/mL) [7], whilst subsequent to the combination of alectinib and semaglutide, only 60% retained plasma

List of abbreviations: $AUC_{0\text{-}10h}$, area under the curve for 0-10 hours; ALK, anaplastic lymphoma kinase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; C_{trough}, trough concentration; C_{max}, maximum concentration; CV, coefficient of variation; CI, confidence interval; GLP-1, glucagon-like peptide 1; NSCLC, non-small cell lung cancer; T_{max}, time until C_{max}.

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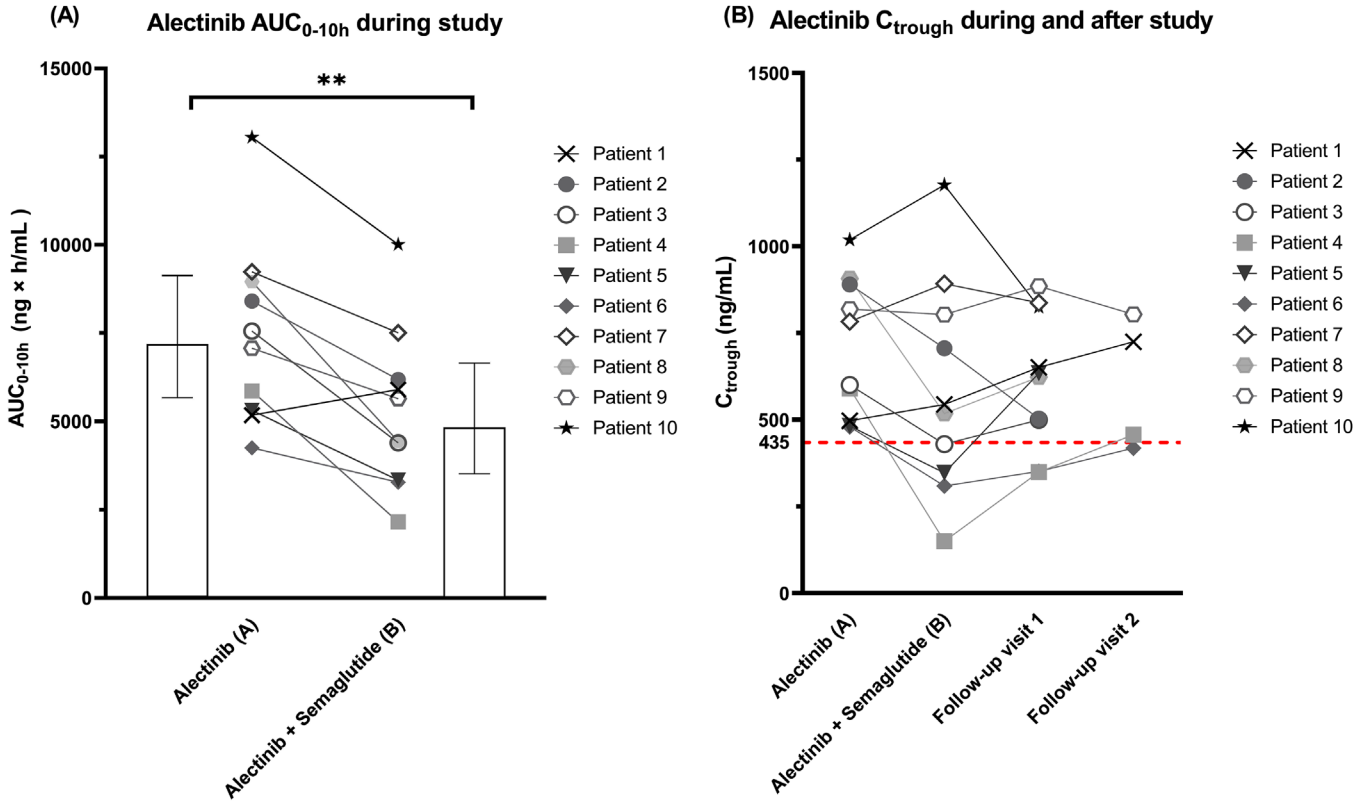

FIGURE 1 Effect of semaglutide on the pharmacokinetics of alectinib. (A) Alectinib individual $AUC_{0\text{-}10h}$ values and geometric mean with 95% CI for study periods A and B. At the y-axis, the alectinib $AUC_{0\text{-}10h}$ geometric mean in ng × h/mL (with 95% CI), is (box-)plotted for alectinib monotherapy (study period A; left bar) and for the combination of alectinib and semaglutide (study period B; right bar). Also, for all 10 patients their individual AUC-value (10 symbols; see legend in the figure) is projected for both study periods (and connected with a line). (B) Change in alectinib trough concentrations of individual patients during (and after) the study. The y-axis represents the alectinib C_{trough} in ng/mL for all individual patients for study period A (alectinib monotherapy), study period B (alectinib + semaglutide), follow-up visit 1 (30 to 84 days after study period B) and follow-up visit 2 (146 to 149 days after study period B). The legend in the figure provides the symbols representing individual patients. The dotted horizontal red line depicts the assumed efficacy-threshold (i.e. 435 ng/mL). $AUC_{0\text{-}10h}$ expressed as geometric mean. ** $P < 0.005$. Patient numbers correspond with the subjects in Supplementary Table S3. Note: During treatment subject 2 was dose-reduced from alectinib 600 mg BID to 450 mg BID; therefore, values after period A are dose-corrected to represent a dose of 600 mg BID. Abbreviations: A, study period A; B, study period B; $AUC_{0\text{-}10h}$, area under the curve 0 to 10 hours; C_{trough}, extrapolated minimum concentration to 12 hours after administration.

levels above the efficacy threshold ($P = 0.125$), see Supplementary Table S3. Plasma samples taken after trial completion demonstrated that in all but 2 patients, C_{trough} levels returned to above the efficacy threshold (i.e. >435 ng/mL) at follow-up visit 1, and only 1 patient remained below the threshold at follow-up visit 2 (Figure 1B).

After the co-administration of semaglutide, patients experienced substantially more toxicity compared to alectinib monotherapy. Gastro-intestinal side-effects such as vomiting (period A versus period B: 0% versus 80%), nausea (period A versus period B: 0% versus 50%), and anorexia (period A versus period B: 0% versus 50%) were more prevalent after administration of semaglutide. All toxicities encompassed grade 1 or 2 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0), see Supplementary Table S4. Review of the patient's diaries revealed a tendency to lower food intake after semaglutide administration.

As this is the first study to describe an interaction between an anti-cancer agent and semaglutide, these findings hold importance for clinicians and cancer patients. As mentioned, for alectinib an exposure-response relationship has been established based on a retrospective analysis [7]. The value of this threshold for progression free survival, is currently studied in a prospective randomized trial; the so-called ADAPT-ALEC study which is accruing patients in the Netherlands and France (NCT05525338) [7]. Given this assumed exposure-response relationship, combining alectinib and semaglutide could potentially hamper the anti-neoplastic efficacy of alectinib. In our study, 4

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out of 10 subjects had trough levels below the 435 ng/mL threshold after the combination of semaglutide and alectinib, compared to none on alectinib monotherapy. All four of these patients were dosed alectinib 450 mg twice daily (BID).

The mechanism of action behind GLP-1 receptor agonists is manifold. In part, the positive effect on weight loss might be due to the induction of satiety by mimicking GLP-1, thereby causing loss of appetite [5]. In addition, GLP-1 receptor agonists reduce gastric motility, resulting in a prolonged sensation of repletion after ingestion of food [5]. This mechanism also causes gastro-intestinal side-effects, such as vomiting. In our trial, nausea and vomiting led to at least one missed dose of alectinib in 5 patients, potentially contributing to the reduction in alectinib $AUC_{0\text{-}10h}$. Nonetheless, most side-effects were transient and only occurred within the first days post-semaglutide administration (Supplementary Figure S1). Notably, all but one missed alectinib dose occurred during the first two days of period B, indicating all patients should have reached steady state concentrations by the time of pharmacokinetic sampling. Additionally, post-hoc sensitivity analysis found no effect of the missed doses on alectinib exposure (Supplementary Table S5). Conversely, a food effect might provide a more plausible hypothesis for the observed reduced alectinib exposure after semaglutide administration. Notably, most patients in our study struggled to adhere to the prescribed diet due to loss of appetite and gastrointestinal adverse events, which are well-known side-effects of semaglutide. Since alectinib is administered orally, its absorption is significantly influenced by food intake [8], in particular since the bioavailability is low (37%), even under fed conditions. Therefore, alterations in food intake will have significant impact on the systemic alectinib exposure. In our study, food (and hence fat) intake was impaired in most patients due to loss of appetite, likely compromising alectinib absorption [8]. This is especially relevant since another study found that patients on semaglutide report having less preference for foods high in fat [9].

In our trial, semaglutide was administered once to assess pharmacokinetic safety. Based on our results, we highlight the need for caution when prescribing semaglutide, especially in alectinib dose-reduced patients. While semaglutide still remains a promising therapy for alectinib-induced weight gain, further research is necessary to evaluate long-term effects of semaglutide on alectinib treatment. For instance, weight loss itself is associated with lower alectinib clearance, which could subsequently increase exposure in the long-term [10].

In conclusion, our study highlights a clinically relevant pharmacokinetic drug-drug interaction between semaglutide and alectinib resulting in a major decrease in alectinib exposure, most likely by a semaglutide-mediated food effect. This underscores the importance of exercising caution when prescribing alectinib and semaglutide (and potentially other GLP-1 receptor agonists) concurrently, and necessitates monitoring of alectinib plasma concentrations in these patients.

AUTHOR CONTRIBUTIONS

Study concept and design: Niels Heersche, Daan A.C. Lanser, Stijn L.W. Koolen, Anne-Marie C. Dingemans, G.D. Marijn Veerman, and Ron H.J. Mathijssen. Study performance: Niels Heersche, Daan A.C. Lanser, Attila Icli, and Peter de Bruijn. Patient selection: Marthe S. Paats and Anne-Marie C. Dingemans. Data analysis and interpretation: Niels Heersche, Daan A.C. Lanser, Esther Oomen-de Hoop, Attila Icli, G.D. Marijn Veerman, and Ron H.J. Mathijssen. Writing–original draft: Niels Heersche, Daan A.C. Lanser, G.D. Marijn Veerman, and Ron H.J. Mathijssen. Writing–review & editing: Niels Heersche, Daan A.C. Lanser, Esther Oomen-de Hoop, Attila Icli, Peter de Bruijn, Marthe S. Paats, Elisabeth F.C. van Rossum, Stijn L.W. Koolen, Ron H.N. van Schaik, Anne-Marie C. Dingemans, G.D. Marijn Veerman, and Ron H.J. Mathijssen.

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All figures were designed in GraphPad Prism version 9.0.2 for Windows, GraphPad Software, Boston, Massachusetts USA, www.graphpad.com.

CONFLICT OF INTEREST STATEMENT

EFCvR is involved in clinical trials with Rhythm Pharmaceuticals for targeted therapy for rare genetic obesity (all paid to the institute). ACD reports grants (all paid to the institute) from Amgen. RHJM reports unrestricted grants for investigator-initiated trials (all paid to the institute) from Astellas, Bayer, Boehringer-Ingelheim, Cristal Therapeutics, Deuter Oncology, Echo Pharmaceuticals, Nordic Pharma, Novartis, Pamgene, Pfizer, Roche, Sanofi, and Servier. None of the other authors reports COIs.

FUNDING INFORMATION

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The competent authority and the local ethics committee of the Erasmus University Medical Center Rotterdam approved the trial (registration ID: NL78079.078.23 and MEC 21-0478, respectively). All participants provided written informed consent prior to their inclusion in the study.

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DATA AVAILABILITY STATEMENT

The data generated in this study are available within the article and its supplementary data files. Raw pharmacokinetic data is available upon request from the corresponding author.

CLINICAL TRIAL REGISTRATION

Dutch Trial Registry ID: NL9702

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REFERENCES

1. Hendriks LE, Kerr KM, Menis J, Mok TS, Nestle U, Passaro A, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(4):339–57.
2. Wu YL, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, et al. Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2024;390(14):1265–76.
3. de Leeuw SP, Pruis MA, Sikkema BJ, Mohseni M, Veerman GDM, Paats MS, et al. Analysis of Serious Weight Gain in Patients Using Alectinib for ALK-Positive Lung Cancer. J Thorac Oncol. 2023;18(8):1017–30.
4. Sikkema BJ, Baart SJ, Paats MS, Smit EF, Schols A, Mathijssen RHJ, et al. Body Weight Gain Associated With Alectinib in Patients With ALK+ Non-Small Cell Lung Cancer: Pooled Analysis of Individual Patient Data From Four Prospective Clinical Trials. J Clin Oncol. 2025;43(6):641–50.
5. Alfaris N, Waldrop S, Johnson V, Boaventura B, Kendrick K, Stanford FC. GLP-1 single, dual, and triple receptor agonists for treating type 2 diabetes and obesity: a narrative review. EClinicalMedicine. 2024;75:102782.
6. Lee ATM, Ou SI, Lisberg A. Letter to Editor. Re "de Leeuw SP, et al. Analysis of Serious Weight Gain in Patients Using Alectinib for ALK Positive Lung Cancer," Semaglutide a Potential Treatment for Serious Weight Gain From ALK Tyrosine Kinase Inhibitors? J Thorac Oncol. 2023;18(9):e97–e9.
7. Groenland SL, Geel DR, Janssen JM, de Vries N, Rosing H, Beijnen JH, et al. Exposure-Response Analyses of Anaplastic Lymphoma Kinase Inhibitors Crizotinib and Alectinib in Non-Small Cell Lung Cancer Patients. Clin Pharmacol Ther. 2021;109(2):394–402.
8. Lanser DAC, de Leeuw SP, Oomen-de Hoop E, de Bruijn P, Paats MS, Dumoulin DW, et al. Influence of Food With Different Fat Concentrations on Alectinib Exposure: A Randomized Crossover Pharmacokinetic Trial. J Natl Compr Canc Netw. 2023;21(6):645–51 e1.
9. Hsu JC, Jaminion F, Guerini E, Balas B, Bordogna W, Morcos PN, et al. Pharmacometric analyses of alectinib to facilitate approval of the optimal dose for the first-line treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer. CPT Pharmacometrics Syst Pharmacol. 2021;10(11):1357–70.
10. Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, et al. Effects of once-weekly semaglutide on appetite, energy

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intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab. 2017;19(9):1242–51.

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