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# Analysis of Serious Weight Gain in Patients Using Alectinib for ALK-Positive Lung Cancer



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## ABSTRACT

**Introduction:** Alectinib is a standard-of-care treatment for metastatic ALK+ NSCLC. Weight gain is an unexplored side effect reported in approximately 10%. To prevent or intervene alectinib-induced weight gain, more insight in its extent and etiology is needed.

**Methods:** Change in body composition was analyzed in a prospective series of 46 patients with ALK+ NSCLC, treated with alectinib. Waist circumference, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle were quantified using *sliceOmatic* software on computed tomography images at baseline, 3 months (3M), and 1 year (1Y). To investigate an exposure-toxicity relationship, alectinib plasma concentrations were quantified. Four patients with more than 10 kg weight gain were referred to Erasmus MC Obesity Center CGG for in-depth analysis (e.g., assessments of appetite, dietary habits, other lifestyle, medical and psychosocial factors, and extensive metabolic and endocrine assessments, including resting energy expenditure).

**Results:** Mean increase in waist circumference was 9 cm (9.7%,  $p < 0.001$ ) in 1Y with a 40% increase in abdominal obesity ( $p = 0.014$ ). VAT increased to 10.8 cm<sup>2</sup> (15.0%,  $p = 0.003$ ) in 3M and 35.7 cm<sup>2</sup> (39.0%,  $p < 0.001$ ) in 1Y. SAT increased to 18.8 cm<sup>2</sup> (12.4%,  $p < 0.001$ ) in 3M and 45.4 cm<sup>2</sup> (33.3%,  $p < 0.001$ ) in 1Y. The incidence of sarcopenic obesity increased from 23.7% to 47.4% during 1Y of treatment. Baseline waist circumference was a positive predictor of increase in VAT ( $p = 0.037$ ). No exposure-

toxicity relationship was found. In-depth analysis ( $n = 4$ ) revealed increased appetite in two patients and metabolic syndrome in all four patients.

**Conclusions:** Alectinib may cause relevant increased sarcopenic abdominal obesity, with increases of both VAT and SAT, quickly after initiation. This may lead to many serious metabolic, physical, and mental disturbances in long-surviving patients.

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**Keywords:** Alectinib; Weight; Body composition; Obesity; Non-small cell lung cancer

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## Introduction

Alectinib is a small-molecule kinase inhibitor (SMKI) approved for treatment of patients with metastatic NSCLC harboring an *ALK* translocation. It has to be taken with food (continental breakfast), as intake without food, or with a low-fat diet, could lead to underexposure to this drug.<sup>1</sup> Alectinib has significantly improved outcome in patients with *ALK*+ NSCLC, with a median progression-free survival of more than 34 months and 5-year overall survival of 62.5% in first-line setting, and is one of the first-line treatment options according to the 2022 European Society for Medical Oncology guideline for *ALK*+ NSCLC.<sup>2,3</sup>

With prolonged survival, low-grade toxicity has more impact on the patient's quality of life, but the mechanisms behind many adverse events of alectinib remain elusive.<sup>4</sup> One of the unexplored side effects is weight gain. The pivotal ALEX trial reported weight gain of any grade in 10% of patients.<sup>5</sup> Nevertheless, this incidence may be underestimated because weight assessment was only mandatory at baseline and actual weights during follow-up were not measured.<sup>5</sup> This probable underreporting is supported by higher incidences (12%–18%) reported in the ALESIA trial and phase 1 and phase 2 trials.<sup>6,7</sup> No data concerning change in weight are mentioned in the J-ALEX and ALUR trials.<sup>8,9</sup>

Currently, little is known about the etiology of alectinib-induced weight gain. Although it is observed during treatment with both *ALK*-specific SMKI's alectinib and lorlatinib (18%–38%), it does not seem to be a class effect because it is not reported for crizotinib, ceritinib, or brigatinib.<sup>2,10–12</sup>

Drug-induced weight gain generally leads to accumulation of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT).<sup>13</sup> Especially VAT is associated with dyslipidemia, insulin resistance, metabolic syndrome, type 2 diabetes mellitus, hypertension, and cardiovascular disease among other obesity-related morbidity.<sup>10</sup> Moreover, obesity can lead to more than 200 chronic diseases, including depression and osteoarthritis.<sup>14,15</sup> Many studies have found that within 5 years of developing obesity, people experience a higher risk for developing a plethora of diseases, a higher risk of experiencing a more severe course of a disease, mental health issues, and even a higher risk of mortality.<sup>16–19</sup> Considering the increasing survival achieved in patients with *ALK*+ NSCLC with the upcoming of highly effective *ALK* inhibitors, prevention of obesity-related diseases is becoming more relevant. Especially, because alectinib is now being studied in a phase 3 trial in the adjuvant setting of stages IB to IIIA *ALK*+ NSCLC.<sup>20</sup>

Regarding the severity of weight gain, there could theoretically be an exposure-toxicity relationship. This

has been described before for other toxicities in osimertinib (EGFR tyrosine kinase inhibitor [EGFR TKI]) treatment.<sup>21</sup> For alectinib-induced weight gain, this is not yet investigated.

In this study, we analyzed changes in body composition of 46 patients from the alectinib cohort of the START-TKI study (NCT05221372, [ClinicalTrials.gov](https://clinicaltrials.gov)) and performed an in-depth investigation of four patients with serious ( $\geq 10$  kg) weight gain developed under treatment with alectinib. The primary aim was to investigate the incidence, severity, and etiology of alectinib-induced changes in body composition after initiation of therapy.

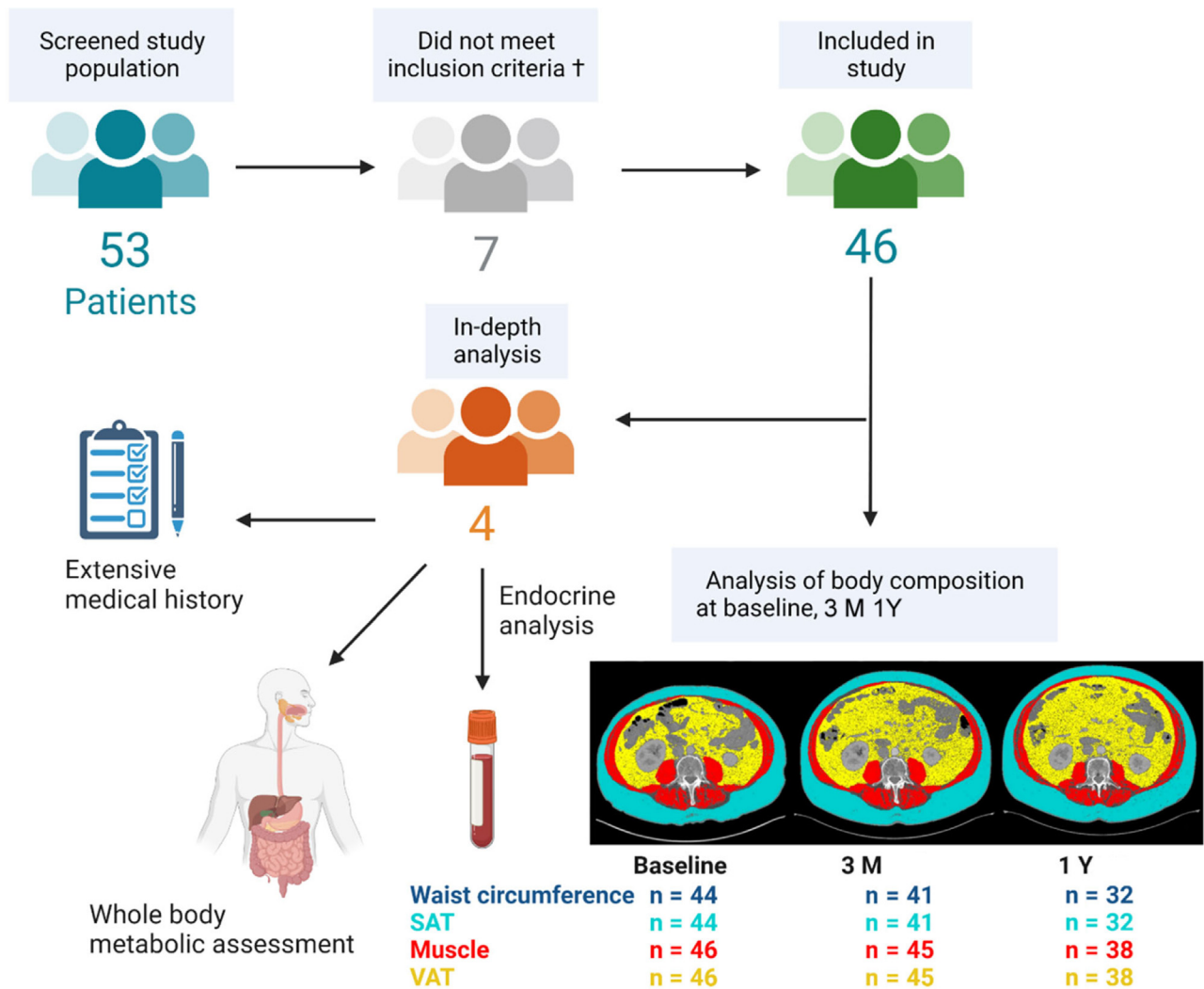
## Materials and Methods

### Study Design

An overview of the study design and procedures is found in [Figure 1](#). All patients from the alectinib cohort of the ongoing prospective biomarker study (START-TKI study, [ClinicalTrials.gov](https://clinicaltrials.gov) NCT05221372), with at least 3 months of therapy and suitable computed tomography (CT) scans for body composition analysis, were eligible for this investigation. CT scans could be analyzed if the third lumbar vertebra (L3) was depicted.<sup>22–24</sup> If the baseline CT or both follow-up scans (3 mo [3M] and 1 y [1Y]) of a patient did not depict L3, the patient was ineligible. Demographics, medical history, and response to therapy were obtained from electronic health records. To investigate an exposure-toxicity relationship, alectinib plasma concentrations were quantified if pharmacokinetic (PK) samples were available. An in-depth analysis at the Erasmus MC Obesity Center was performed in a subset of patients with more than or equal to 10 kg weight gain, comprising a profound endocrine and dietary assessment.

### Body Composition Analysis

On-treatment contrast-enhanced CT scans at baseline, 3M, and 1Y after start of treatment were analyzed for changes in body composition using *sliceOmatic* software (version 5.0, TomoVision, Montreal, Canada) ([Supplementary Appendix: Fig. 1](#)). The abdominal perimeter measured at L3 provided an accurate estimation of waist circumference.<sup>25</sup> Abdominal obesity was defined as waist circumference greater than or equal to 102 cm for males or greater than or equal to 88 cm for females.<sup>26</sup> *SliceOmatic* performs reliable quantification of VAT, SAT, and skeletal muscle (SM) on CT scans, when measured cross-sectionally at the level of L3.<sup>22,23</sup> VAT was divided by SM to calculate the VAT/SM index, with sarcopenic obesity defined as VAT/SM index greater than



**Figure 1.** Study design. Overview of patient selection and study procedures. <sup>†</sup>CT scans unusable (L3 not reached, n = 5) or cessation of treatment within 3 months (n = 2). <sup>‡</sup>3 months follow-up scan (n = 1) or 1 year follow-up scan (n = 3) was excluded when L3 was not imaged. SAT and waist circumference were excluded from all analyses when the CT image contained only part of the subcutaneous tissue and abdominal perimeter at baseline (n = 2). SAT and waist circumference were excluded from 3 months (n = 2) or 1 year (n = 4) follow-up if not completely depicted at this time point only. CT, computed tomography; L3, third lumbar vertebra; SAT, subcutaneous adipose tissue.

1.25.<sup>27</sup> Waist circumference and SAT were excluded if the CT image displayed only a part of these parameters.

Segmentation was performed by SPdL after training by an experienced user, using pre-established thresholds of Hounsfield units in accordance with previous research (SM -29 to +150, VAT -150 to -50, SAT -190 to -30).<sup>28</sup>

To ensure data quality and integrity, 20% of the cases were segmented by a second observer (MAP), with analysis of interobserver variation afterward. SPdL analyzed 20% of cases twice to test for intraobserver variation.

### PK Sampling

Alectinib plasma concentrations were quantified by a validated assay.<sup>29</sup> Samples were suitable if the time

between last dose and blood withdrawal ( $\Delta T$  in formula) was at least 5 hours ( $T_{max}$ ). The trough plasma concentration (i.e., immediately before administration of the next dose) was calculated using the following formula:  $C_{trough} = C_{sample} * e^{(-\Delta T * \frac{0.693}{53})}$ .

### In-Depth Analysis

Four patients were selected from the cohort on the basis of their substantial weight gain since start of therapy ( $\geq 10$  kg) and were referred to the endocrinologist at the academic Erasmus MC Obesity Center CGG, a European expertise center for tertiary obesity care. Diagnostic workup of potential causes and contributing factors of weight gain, including an endocrine, metabolic,

psychosocial, and lifestyle analysis, was performed. The in-depth analysis included an extensive medical evaluation with history and physical examination, hormonal and metabolic assessment, bioelectrical impedance measurements (Inbody S10, BioSpace, Seoul, Republic of Korea), and measurement of resting energy expenditure using indirect calorimetry (Q-NRG, Cosmed, Roma, Italy).

The medical evaluation evaluated many potential causal factors of weight gain and other symptoms of underlying conditions which can contribute to weight gain, including questions about appetite and satiety, lifestyle, and dietary habits.<sup>30</sup> Venous overnight-fasted blood samples were drawn and analyzed as part of standard clinical care using routine laboratory measurements. These included the following: serum insulin, glucose, glycated hemoglobin A1c, leptin, plasma lipids (triglyceride level; high density lipoprotein-cholesterol [HDL-c], low density lipoprotein-cholesterol), aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, thyroid-stimulating hormone, free thyroxine and, in males, testosterone. Free testosterone levels were calculated on the basis of sex-hormone binding globulin levels using Vermeulen's formula.<sup>31</sup> Leptin levels were determined with commercially available enzyme-linked immunosorbent assay kits (Mediagnost, Reutlingen, Germany). Predicted resting energy expenditure was calculated using the Harris-Benedict formula.<sup>32</sup>

Insulin resistance was determined using the homeostasis model assessment of insulin resistance (HOMA-IR):  $\text{HOMA-IR} = [\text{fasting insulin } (\mu\text{U/mL})] * [\text{fasting glucose } (\text{mmol/L})] / 22.5$ , and it was defined as HOMA-IR greater than 2.<sup>33,34</sup> Metabolic syndrome was defined using standard criteria.<sup>35</sup> Reference values for fat-free mass index (FFMI) corrected for body mass index (BMI) and fat mass index (FMI) were obtained from population studies.<sup>36,37</sup>

### Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 28.0.1.0. Normally distributed data were reported as mean plus or minus SD and analyzed using *t* tests. Non-normally distributed data were reported as median with interquartile range (IQR) and analyzed using related-sample Wilcoxon signed rank and Mann-Whitney *U* tests. Correlations between variables were tested using Spearman rank correlation or Pearson correlation. Significant correlations were tested subsequently with multivariable logistic regression. For change in proportions, the McNemar test was used. Interobserver and intraobserver variation was tested using the intraclass correlation coefficient (absolute agreement).

## Results

### Study Population

Baseline characteristics and patient selection are found in [Table 1](#) and [Figure 1](#). In total, 46 patients were included in the analysis, and 3M and 1Y follow-up were available for 45 (98%) and 38 (83%) patients, respectively, with complete follow-up in 37 (80%). Waist circumference and SAT were available in 42 patients (91%) at 3M and 32 patients (70%) at 1Y.

### Change in Body Composition During Follow-Up

All results and an example of one patient are found in [Table 1](#), [Figures 2 to 4](#), and the [Supplementary Appendix](#). As presented in [Table 1](#), waist circumference increased with  $3.3 \pm 6.3$  cm (3.7%,  $p < 0.001$ ) in 3M,  $9.0 \pm 6.1$  cm (9.7%,  $p < 0.001$ ) in 1Y follow-up, and  $4.4 \pm 7.4$  cm (4.7%,  $p = 0.003$ ) between 3M and 1Y ([Figs. 1B](#) and [2A](#)). The incidence of abdominal obesity increased from 46.9% at baseline to 65.6% at 1Y follow-up (relative difference +40%,  $p = 0.014$ ). No baseline characteristics correlated with the change in waist circumference.

VAT increased to  $10.8 \text{ cm}^2$  (IQR:  $-3.0$  to  $36.2$ ) in 3M (15.0%,  $p = 0.003$ ) and  $35.7 \text{ cm}^2$  (IQR:  $16.2$ – $94.6$ ) in 1Y (39.0%,  $p < 0.001$ ) ([Fig. 2C](#)). Between 3M and 1Y, increase in median VAT was +23.9% ( $p < 0.001$ ) with an absolute increase of  $28.7 \text{ cm}^2$  (IQR:  $2.3$ – $47.2$ ). In 22 patients (57.9%), VAT increased greater than 30% in 1Y, with a median of  $59.7 \text{ cm}^2$  (IQR:  $23.6$ – $124.3$ ). Of all baseline characteristics, only waist circumference and VAT significantly correlated with  $\Delta\text{VAT1Y}$ . Multivariable logistic regression ([Fig. 4](#)) revealed baseline waist circumference to be a significant predictor of absolute  $\Delta\text{VAT1Y}$  ( $\beta = 0.622$ ,  $p = 0.037$ ).  $\Delta\text{VAT1Y}$  was significantly higher in patients with abdominal obesity at baseline ( $59 \text{ cm}^2$  versus  $22 \text{ cm}^2$  in nonobese patients,  $p = 0.008$ , [Supplementary Appendix: Table 1 and Fig. 2](#)).

SAT increased to  $18.8 \pm 32.1 \text{ cm}^2$  in 3M (12.4%,  $p < 0.001$ ),  $45.4 \text{ cm}^2$  (IQR:  $17.2$ – $85.0$ ) in 1Y (33.3%,  $p < 0.001$ ), and  $34.8 \pm 52.3 \text{ cm}^2$  between 3M and 1Y (+21.3%,  $p < 0.001$ ) ([Fig. 2D](#)). In 18 patients (56.3%), SAT increased greater than 30%, with a median of  $76.5 \text{ cm}^2$  (IQR:  $47.1$ – $120.2$ ). No baseline characteristics correlated with the change in SAT. There was a positive correlation between the change in waist circumference in 1 year ( $\Delta\text{WC1Y}$ ) and  $\Delta\text{SAT1Y}$  ( $\rho = 0.801$ ,  $p < 0.001$ ),  $\Delta\text{WC1Y}$  and  $\Delta\text{VAT1Y}$  ( $\rho = 0.673$ ,  $p < 0.001$ ), and  $\Delta\text{VAT1Y}$  and  $\Delta\text{SAT1Y}$  ( $\rho = 0.490$ ,  $p = 0.004$ ) ([Supplementary Appendix: Figs. 3 and 4](#)).

There was no significant change in SM mass during follow-up ([Fig. 2E](#)). Median VAT/SM index increased from 0.7 (IQR:  $0.4$ – $1.3$ ) at baseline to 1.1 (IQR:  $0.6$ – $2.1$ ) at 1Y ( $p < 0.001$ ), with a rise in the incidence of sarcopenic obesity from 24% to 47% ( $p = 0.003$ ).

Table 1. Body Composition Analysis

Characteristics	N = 46 <sup>a</sup>	Relative Difference
<b>Baseline characteristics</b>		
Age	60 ± 12.7	
Female sex	25 (54%)	
ECOG Performance status ≤ 1	36 (78%)	
Smoker (former or active)	15 (33%)	
Hypertension	9 (20%)	
Diabetes mellitus	2 (4%)	
Dyslipidemia	4 (9%)	
Alectinib as first-line therapy	35 (76%)	
Brain or LM metastases at baseline	10 (19%)	
<b>Days between CT and start therapy</b>		
Baseline CT (days before start of therapy)	26 [14-38]	
3 mo follow-up CT (n = 45)	85 [83-93]	
1 y follow-up CT (n = 38)	362 [345-394]	
<b>Baseline body composition</b>		
Waist circumference in cm (n = 44)	94 ± 12	
SM surface area in cm <sup>2</sup>	127 ± 29	
VAT surface area in cm <sup>2</sup>	90 [50-173]	
VAT/SM index	0.7 [0.4-1.3]	
SAT surface area in cm <sup>2</sup> (n = 44)	184 ± 82	
<b>Change during first 3 mo in cm<sup>2</sup> (%)</b>		
Waist circumference in cm (%) (n = 41)	+3.3 ± 6.3	+3.7%, p < 0.001
SM (n = 45)	+0.6 ± 9.5	+0.8%, p = 0.699
VAT (n = 45)	+10.8 [-3.0 to +36.2]	+15.0%, p = 0.003
VAT/SM index (n = 45)	0.8 [0.5-1.5]	+10.8%, p = 0.007
SAT (n = 41)	+18.8 ± 32.1	+12.4%, p < 0.001
<b>Change during first year in cm<sup>2</sup> (%)<sup>b</sup></b>		
Waist circumference in cm (%) (n = 32)	+9.0 ± 6.1	+9.7%, p < 0.001
SM (n = 38)	-0.8 ± 12.1	-0.41%, p = 0.671
VAT (n = 38)	+35.7 [16.2-94.6]	+39.0%, p < 0.001
VAT/SM index (n = 38)	1.1 [0.6-2.1]	+48.7%, p < 0.001
SAT (n = 32)	+45.4 [17.2-85.0]	+33.3%, p < 0.001
<b>Incidence of abdominal obesity<sup>c</sup></b>		
Baseline (n = 44)	47.7% (21/44); 46.3% (19/41); 46.9% (15/32) <sup>d</sup>	
3 mo (n = 41)	56.1% (23/41)	+21%, p = 0.102 <sup>b</sup>
1 y (n = 32)	65.6% (21/32)	+40%, p = 0.014 <sup>b</sup>
<b>Incidence of sarcopenic obesity<sup>e</sup></b>		
Baseline	23.9% (11/46); 24.4% (11/45); 23.7% (9/38) <sup>d</sup>	
3 mo (n = 45)	35.6% (16/45)	+45.5%, p = 0.059 <sup>b</sup>
1 y (n = 38)	47.4% (18/38)	+100%, p = 0.003 <sup>b</sup>
<b>Best response</b>		
Partial response	83% (38/46)	
Stable disease	13% (6/46)	
Mixed response	2% (1/46)	
Unknown	2% (1/46)	
<b>Follow-up</b>		
Median duration of follow-up	34 mo [25-50]	
Median time on treatment	Not reached	
<b>Toxicity</b>		
At least one dose reduction	52% (24/46)	

(continued)

Table 1. Continued

Characteristics	N = 46 <sup>a</sup>	Relative Difference
Reasons for discontinuation (n = 11)		
Progressive disease	82% (9/11)	
Toxicity	9% (1/11)	
Unknown	9% (1/11)	

Note: Numeric variables are reported as mean  $\pm$  SD or median [IQR] depending on normality. The relative difference was calculated using the paired *t* test, related-sample Wilcoxon signed rank test, or McNemar test. Response was defined according to the RECIST criteria version 1.1.

<sup>a</sup>n = 46 unless mentioned otherwise.

<sup>b</sup>Compared with baseline.

<sup>c</sup>Defined as waist circumference  $\geq$ 102 cm for males or  $\geq$ 88 cm for females.<sup>26</sup>

<sup>d</sup>Cases excluded in pairwise comparisons when only available at baseline.

<sup>e</sup>Defined as VAT/SM index  $>$  1.25.<sup>27</sup>

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; n, number of patients; SAT, subcutaneous adipose tissue; SM, skeletal muscle; VAT, visceral adipose tissue.

Testing for intraobserver and interobserver variability revealed excellent reliability for all body composition variables, with intraclass correlation coefficients greater than or equal to 0.994 (see [Supplementary Appendix: Table 2](#)).

### PK Measurements

Appropriate PK samples of 3M and 1Y follow-up were available for 16 and 18 patients, respectively. Mean trough concentration ( $C_{\text{trough}}$ ) was  $652 \pm 263$  ng/mL in the first 3 months and  $581 \pm 219$  ng/mL during 1Y follow-up. There was no correlation between  $C_{\text{trough}}$  and change in waist circumference, VAT, or SAT during 3M or 1Y follow-up (see [Supplementary Appendix: Figs. 5–7](#)).

### In-Depth Analysis

We performed an in-depth analysis of four patients with remarkable (10–30 kg) weight gain during alectinib treatment. An overview of all data is found in [Table 2](#) and [Supplementary Appendix](#).

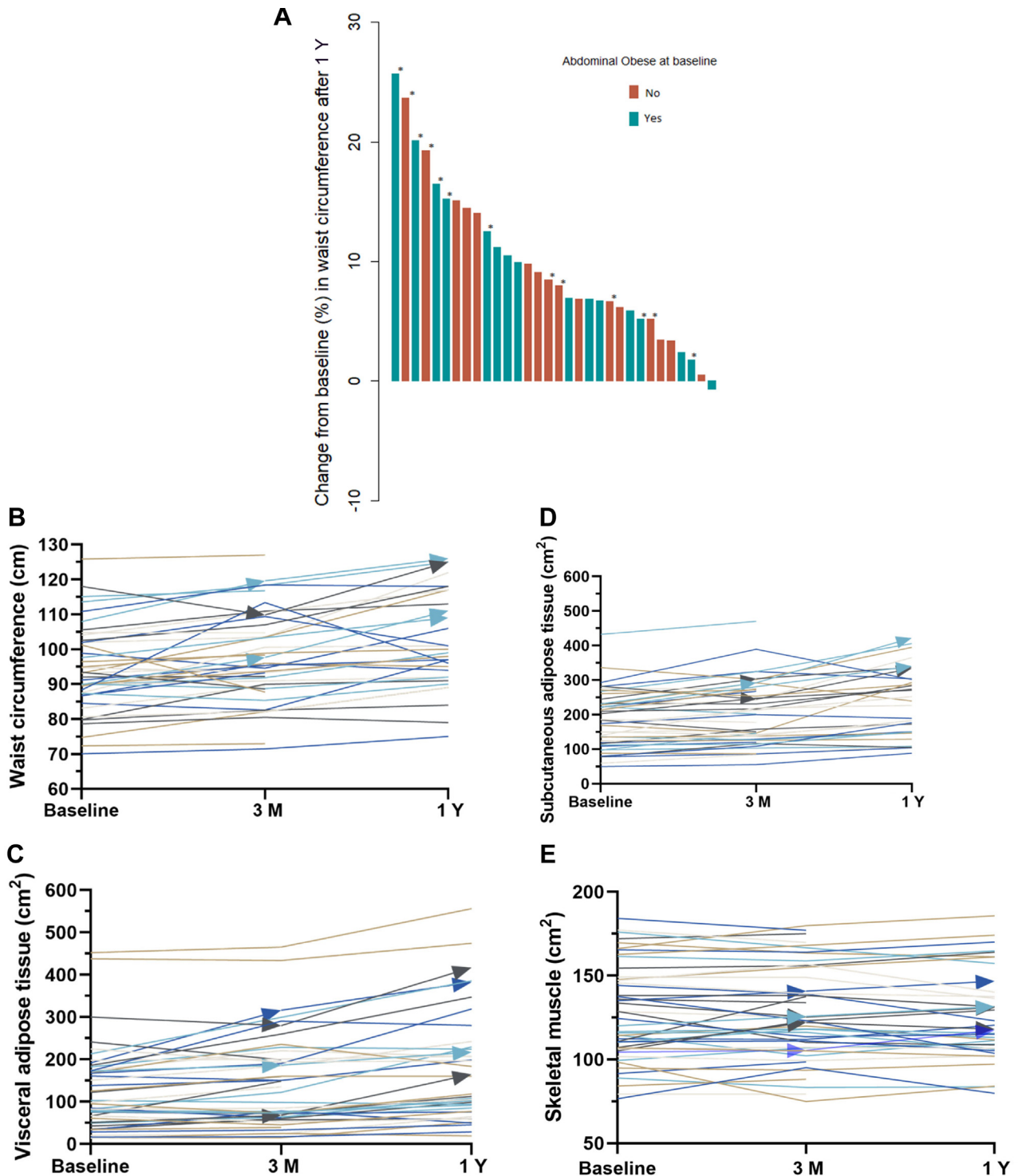
**Patient A.** In a 54-year-old male, weight increased from 93 kg (BMI 29.4 kg/m<sup>2</sup>) to 98.5 kg after 2 months of alectinib therapy and to 112 kg (+20%, BMI 35.3 kg/m<sup>2</sup>) after 11 months of treatment. He reported increased appetite since initiation of alectinib. After 15 months of treatment, we saw a patient with abdominal-type obesity, low FFMI of 21.2 (BMI adjusted: 10th percentile), and high FMI of 11.8 (95th percentile). During alectinib treatment, he developed metabolic syndrome on the basis of waist circumference greater than or equal to 102 cm, grade 1 hypertriglyceridemia, and grade 1 hypertension.

**Patient B.** A 20-year-old male with baseline weight of 75 kg (BMI 25.2 kg/m<sup>2</sup>) experienced weight gain to 81 kg (BMI 27.2 kg/m<sup>2</sup>) in 6 months, 102 kg (+36%, BMI 34.2 kg/m<sup>2</sup>) in 1 year, and 106 kg (+41%, BMI 35.5 kg/m<sup>2</sup>)

in 2 years, with increased appetite since start of alectinib. Assessment after 20 months of therapy revealed abdominal and generalized obesity, low FFMI (20.9, BMI adjusted: fifth percentile), and high FMI (13.1, 95th percentile). Endocrine analysis revealed elevated leptin level, insulin resistance (HOMA-IR 13.2), and decreased testosterone level (normogonadotropic hypogonadism, most likely secondary to the abdominal obesity). During alectinib treatment, this patient met the criteria of metabolic syndrome on the basis of waist circumference greater than or equal to 102 cm, grade 2 hypertension, and grade 1 hypertriglyceridemia. Metformin was started to reduce insulin resistance, inhibit the increased appetite, and facilitate weight loss. Interestingly, this patient experienced profound weight loss ( $\pm$ 10 kg in 5 mo) after initiation of metformin.

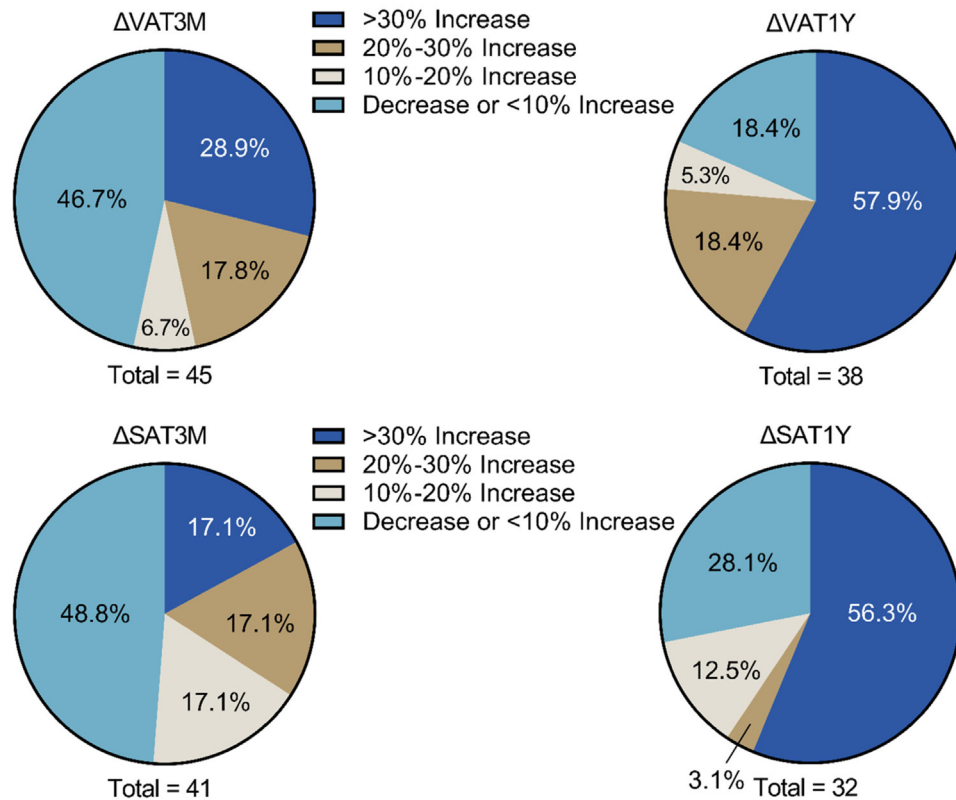
**Patient C.** In a 68-year-old female, weight raised from 93 kg (BMI 31.1 kg/m<sup>2</sup>) at baseline to 104 kg (+12%, BMI 34.7 kg/m<sup>2</sup>) in 1 year and to 106 kg (BMI 35.4 kg/m<sup>2</sup>) in 2 years. Investigation after 27 months of therapy revealed abdominal and generalized obesity, low FFMI (16.7, BMI adjusted: fifth percentile), and high FMI (8.2, 50th percentile). Hormonal analysis revealed insulin resistance (HOMA-IR 6.2). After initiation of alectinib, this patient met the criteria of metabolic syndrome on the basis of waist circumference greater than or equal to 88 cm, grade 2 hypertriglyceridemia, grade 3 hypertension, and HDL-c less than 1.3 mmol/L.

**Patient D.** In a 54-year-old female, weight increased from 69 kg (BMI 29.8 kg/m<sup>2</sup>) at baseline to 79 kg (+14%, BMI 34.1 kg/m<sup>2</sup>) after 2 years. Additional analyses after 3 years and 2 months of treatment revealed abdominal obesity, low FFMI (18, BMI adjusted: 25th percentile) and high FMI (16.9, 95th percentile), elevated leptin level, and insulin resistance (HOMA-IR 7.2). After initiation of alectinib, this patient met the criteria of



**Figure 2.** Body composition over time. (A) Waterfall plot changes in waist circumference after 1Y. (B) Waist circumference. (C) Visceral adipose tissue. (D) Subcutaneous adipose tissue. Change in body composition. The waterfall plot of waist circumference (A) shows the percentual change in waist circumference between baseline and 1Y treatment of alectinib (change in mean waist circumference:  $9.0 \pm 6.1$  cm, 9.7%,  $p < 0.001$ ) \*Indicates subjects in whom the dose of alectinib is adjusted during the first year. Waist circumference (B), visceral adipose tissue (C), subcutaneous adipose tissue (D) and skeletal muscle (E) per time point for each patient. The spaghetti plots visualize the increase of waist circumference, visceral adipose tissue (in 3M  $10.8$  cm<sup>2</sup> [IQR  $-3.0$  to  $36.2$ ], +15.0%,  $p = 0.003$ , in 1Y  $35.7$  cm<sup>2</sup> [IQR:  $16.2$ - $94.6$ ], +39.0%,  $p < 0.001$ ), subcutaneous adipose tissue (in 3M  $18.8 \pm 32.1$  cm<sup>2</sup>, +12.4%,  $p < 0.001$ , in 1Y  $45.4$  cm<sup>2</sup> [IQR:  $17.2$ - $85.0$ ], +33.3%,  $p < 0.001$ ) throughout the first year of treatment with alectinib treatment. The subjects ( $n = 4$ ) in whom an in-depth analysis is performed are indicated with an arrow. 1Y, 1 year; 3M, 3 months; IQR, interquartile range.





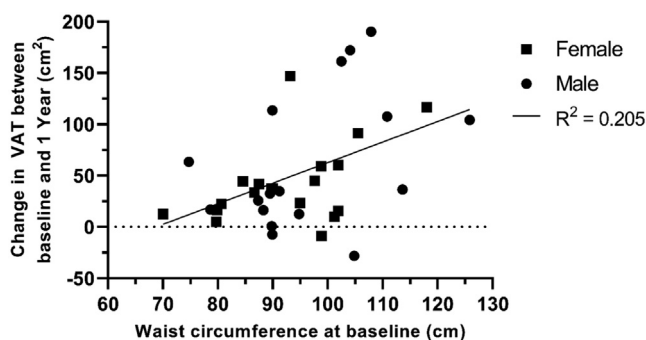
**Figure 3.** Change in visceral and subcutaneous adipose tissue in % per time point. Pie charts of change in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) per timepoint, categorized in percentage change. SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; ΔSAT1Y = change of SAT in first year; ΔSAT3M = change of SAT in first 3 months; ΔVAT1Y = change of VAT in first year; ΔVAT3M = change of VAT in first 3 months.

metabolic syndrome on the basis of waist circumference greater than or equal to 88 cm, grade 1 hypertriglyceridemia, and HDL-c less than 1.3 mmol/L.

### Discussion

Our study reveals that most of the patients undergo a considerable increase in waist circumference and

adipose tissue after initiation of alectinib therapy. This phenomenon starts within the first months of therapy and is accompanied by an impressive +40% relative difference in the incidence of abdominal obesity. Consistent with these findings, the in-depth analysis found metabolic complications in all four patients. Considering the prolonged life expectancy resulting from alectinib therapy, patients with ALK-positive NSCLC might gradually develop one of the more than 200 known obesity-related diseases, including type 2 diabetes mellitus, cardiovascular comorbidity, depression, or osteoarthritis.<sup>16-19</sup> Complications, such as a low quality of life partially because of physical impairments, the obesity stigma, mental health issues, an increased risk of severe course of infections (e.g., coronavirus disease 2019 and influenza), thrombosis, hypoxemia, and many other diseases, can already be present as soon as the obesity, in particular abdominal fat accumulation, has developed.<sup>38-40</sup> In addition, several patients reported the need for wider clothing contributing to pre-existing financial toxicity of their anticancer treatment. In other types of cancer, obesity is even related to worse clinical outcomes of anticancer therapy, such as cancer recurrence, prognosis, and increased risks of treatment-



**Figure 4.** Linear regression plot of baseline waist circumference and change in VAT during 1 year. Scatterplot of baseline waist circumference (cm) and change in VAT during first year, with linear regression line ( $R^2$ ). VAT, visceral adipose tissue.

Table 2. In-Depth Analysis

Subjects	Patient A	Patient B	Patient C	Patient D
Gender	Male	Male	Female	Female
Age, y	54	20	68	54
Dose, mg	450 b.i.d.	600 b.i.d.	600 b.i.d.	600 b.i.d.
Baseline weight, kg	93 (BMI 29.4)	75 (BMI 25.2)	93 (BMI 31.1)	69 (BMI 29.8)
Weight, kg, 2 y	109 (+17%, BMI 34.4)	106 (+41%, BMI 35.5)	106 (+14%, BMI 35.4)	79 (+14%, BMI 34.1)
Obesity type	Abdominal	Abdominal, generalized	Abdominal, generalized	Abdominal
Appetite	Increased	Increased	Normal, unchanged	Normal, unchanged
Bioelectrical impedance analysis	FFMI 21.2 (10th pc), FMI 11.8 (95th pc)	FFMI 20.9 (5th pc), FMI 13.1 (95th pc)	FFMI 16.7 (5th pc), FMI 8.2 (50th pc)	FFMI 18 (25th pc), FMI 16.09 (95th pc)
Resting energy expenditure	1985 kcal/d (94% of expected)	2114 kcal/d (94% of expected)	2011 kcal/d 121% of expected	1430 kcal/d 99% of expected
Cortisol, nmol/L	Saliva: 0.6 (ref 1.6-19.3) 24H Urine: 22	Saliva: <0.5 24H Urine: 16	Saliva: 1.4 (ref <2.8) 24H Urine: 14	Saliva 7.7 (ref 1.6-19.3) 24H Urine: 10
TSH, mU/L	TSH: 1.34 (ref 0.56-4.27)	TSH: 4.85 (ref 0.56-4.27)	TSH: 1.09 (ref 0.56-4.27)	TSH: 1.22 (ref 0.56-4.27)
FT4, pmol/L	FT4: 19.3 (ref 13.5-24.3)	FT4: 22.4 (ref 13.5-24.3)	FT4: 19.5 (ref 13.5-24.3)	FT4: 23.6 (ref 13.5-24.3)
Fasting leptin, $\mu\text{g/L}$	8.4 (ref 0.2-12.4)	43.7 (ref 0.2-12.4)	30.5 (ref 1.5-33.9)	79.2 (ref 1.5-33.9)
Fasting insulin, pmol/L	40 (ref <100)	363 (ref <100); HOMA-IR 13.2	171 (ref <100); HOMA-IR 6.2	209 (ref <100); HOMA-IR 7.2
Fasting blood glucose, mmol/L	5.3 (ref 4.0-6.1)	5.7 (ref 4.0-6.1)	5.7 (ref 4.0-6.1)	5.4 (ref 4.0-6.1)
$\Delta\text{WC1Y}$ , cm (%)	+17.8 (+16.5%)	+21.3 (+23.7%)	+6.9 (+5.8%)	+10.9 (+11.1%)
$\Delta\text{VAT1Y}$ , $\text{cm}^2$ (%)	+190.3 (+99.3%)	+113.7 (+223.9%)	+116.8 (+38.9%)	+44.8 (+26.0%)
$\Delta\text{SAT1Y}$ , $\text{cm}^2$ (%)	+92.1 (+37.6%)	+190.8 (+82.6%)	+51.5 (+18.2%)	+119 (+53.8%)
$\Delta\text{SM1Y}$ , $\text{cm}^2$ (%)	+11.6 (+8.6%)	-2.6 (-1.9%)	+10.9 (+10.2%)	+11.4 (+9.5%)

Note: The complete overview can be found in [Supplementary Table 1](#).

24H, 24-hour portion;  $\Delta\text{...3M}$ , change in SM/SAT/VAT/WC first 3 months;  $\Delta\text{...1Y}$ , change in SM/SAT/VAT/WC in first year; b.i.d., twice a day; BMI, body mass index; FFMI, fat-free mass index; FMI, fat mass index; m, months; pc, percentile; ref, reference value; SAT, subcutaneous adipose tissue; SDR, second-degree relative; SHBG, sex-hormone binding globulin; SM, skeletal muscle; VAT, visceral adipose tissue; WC, waist circumference.

related problems.<sup>41–48</sup> Though the historical focus on weight loss in patients with lung cancer remains relevant, caregivers should pay more attention to SMKI-related weight gain. Withal, we ought to pay more attention to (low-grade) longitudinal toxicity in general, considering the negative impact this has on patients' quality of life.<sup>4</sup>

Nearly every patient in this study experienced some increase of waist circumference during the follow-up. Prior research revealed that waist circumference and BMI are strongly correlated.<sup>49</sup> If we would apply this to our results, the incidence of weight gain would be considerably higher than the proportion of patients reported in the ALEX registration trial and phase 2 studies.<sup>5,6</sup> This finding is consistent with the suspected underreporting in the ALEX trial as assessment of weight was not mandatory during follow-up. In addition, weight gain as a side effect might be overlooked by treating physicians because ALK fusion occurs in only a few percent of NSCLC, resulting in a relatively low exposure to patients treated with alectinib for a single physician.<sup>50</sup>

On top of increased waist circumference, body composition seems to deteriorate as well after initiation of alectinib. In 57.9% of patients, VAT increased more than 30% with a median increase of 59.7 cm<sup>2</sup>. Accumulated VAT is an important factor in obesity-associated diseases.<sup>14</sup> Per 10 cm<sup>2</sup> increase in VAT, the odds for metabolic syndrome and hypertriglyceridemia increased with 23% and 30%, respectively, in a population study.<sup>51</sup> In line with this hypothesis, our in-depth analysis found metabolic syndrome in all four patients.

Because muscle mass does not expand whereas both VAT and SAT increase, a very unhealthy form of weight gain arises with an important increase in the incidence of sarcopenic obesity.<sup>27</sup> Sarcopenic obesity is associated with an even higher incidence of insulin resistance, physical disability, and lower quality of life than obesity with regular muscle mass.<sup>22,27,52</sup>

Consequently, patients experiencing alectinib-induced weight gain might benefit from expert obesity care. Exercise and caloric restriction could lower VAT and prevent metabolic complications.<sup>53</sup> Furthermore, treatment with metformin, which can decrease appetite at the hypothalamic level, led to profound weight loss in one patient.<sup>54</sup> The effect of combined lifestyle intervention and medical antiobesity treatment on alectinib-induced obesity therefore ought to be further investigated.<sup>55,56</sup> In addition, follow-up should be extended to assess body composition and obesity-related complications in the longer run.

Undoubtedly, prevention is preferable over treatment. Risk stratification, with close weight monitoring in high-risk patients, promotes early recognition and interventions to prevent escalation.<sup>57</sup> Baseline waist circumference was a positive predictor of the increase in

VAT and could therefore be used as a parameter for baseline risk stratification. During follow-up, the severity of body fat increase can be assessed using waist circumference as well, because  $\Delta$ WC1Y strongly correlates with both  $\Delta$ VAT1Y and  $\Delta$ SAT1Y. Evidently, weight assessment at each outpatient visit is recommended too, because BMI correlates with both VAT and SAT.<sup>14,49</sup>

A relationship between alectinib exposure and change in body composition was not found. The small sample size with unavailability of usable PK samples in most patients may have contributed to this outcome. Nevertheless, a clear exposure-toxicity relationship might not be apparent in alectinib therapy.<sup>58</sup>

Little is known about the etiology of alectinib-induced weight gain. Two of four patients in the in-depth analysis experienced a notable increase in appetite. Disturbances of endocrine regulators of appetite (e.g., ghrelin, cholecystokinin, peptide YY, glucagon-like peptide 1, leptin) could be the underlying mechanism and are therefore of interest for future investigations. The elevated leptin level found in two of four patients is thought to be secondary to the observed weight gain. Nevertheless, as baseline leptin level is unknown, it is possible that alectinib treatment leads to leptin resistance, resulting in increased appetite.

As mentioned before, weight gain is less likely to be a class effect of ALK inhibitors. Nevertheless, the higher incidence of nausea and diarrhea found in crizotinib, ceritinib, and brigatinib may prevent therapy-induced weight gain.<sup>11,12,59</sup> In patients treated with lorlatinib, hypercholesterolemia and hypertriglyceridemia are frequently reported adverse events, which often require lipid-lowering medications or dose adjustments of previously started medication. These AEs are not associated with alectinib therapy. Weight increase is another frequently (18%–38%) documented adverse event in patients treated with lorlatinib. No exposure-safety relationship was identified between lorlatinib plasma exposure and weight gain grade greater than or equal to 2.<sup>60</sup> A number of patients have actively communicated an increase of appetite after the initiation of lorlatinib.<sup>61</sup> Notably, this is also reported by some patients in the present study. Because the increase of appetite is not systematically collected, this might be an interested avenue for future research.

Interestingly, genetic deletion of the ALK gene led to thinness in mice, and intronic ALK variants are associated with thinness in humans.<sup>62</sup> Besides ALK, alectinib has inhibitory potential against the Rearranged during Transfection (RET) oncogene, although not enough for therapeutic efficacy.<sup>63</sup> RET is involved in body weight regulation as signaling receptor for growth and differentiation factor 15 and GDNF receptor alpha-like, both highly active in the brain.<sup>64</sup> Nevertheless, drug-induced

weight gain is not reported in RET inhibitor selpercatinib, and this underlying mechanism would not explain lorlatinib-induced weight gain.<sup>65</sup>

Likewise, dysregulation of mammalian target of rapamycin (mTOR), a kinase downstream of ALK, is associated with obesity and diabetes.<sup>10,66</sup> Nonetheless, if mTOR imbalance was the sole cause of alectinib-induced weight gain, this phenomenon would be expected in many SMKIs.

The study design yields some limitations, such as the limited number of patients and the fact that it was performed in a single center. Furthermore, in the prospective START-TKI trial, all data are collected as part of standard care and can therefore be incomplete at the point of analyses, resulting in scarce weight data in our study. Nevertheless, we found that changes in body composition can be assessed without weight data using regular-care CT scans.

The in-depth analysis is valuable as it excludes several conditions and factors that drive weight gain and indicates that specific endocrine disturbances are occurring among patients using alectinib.<sup>30</sup> Nevertheless, because there are no baseline values for all measurements, the true change cannot be determined.

More extensive insight in the underlying mechanisms of weight gain associated with alectinib therapy is needed to determine the right strategy to prevent or limit weight gain. Recently, a large, multicenter, prospective trial (NCT05525338) has started in which weight and laboratory parameters including appetite and satiety hormones are collected.<sup>67</sup>

In conclusion, our study supports the observation that alectinib induces weight gain, and the effects seem to be much greater than anticipated. Alectinib-induced weight gain might be underreported in previous trials and underestimated by caregivers. In most patients, this side effect occurs within 3 months after initiation of therapy, with progression thereafter. In addition, there is a discrepancy between the increase in adipose tissue and muscle mass, leading to sarcopenic obesity. Therefore, alectinib-induced weight gain may lead to metabolic complications and numerous other obesity-related conditions and lower quality of life in long-surviving patients. Our in-depth analysis revealed increased appetite in two and metabolic syndrome in all four patients, though the exact underlying mechanisms remain unclear. Additional research to investigate the etiology is needed.

## CRediT Authorship Contribution Statement

**Simon P. de Leeuw:** Conceptualization, Data curation, Formal analysis, Investigation (body composition analysis), Methodology, Project administration, Writing—original draft, Writing—revisions, Data

interpretation, Critical reviewing of the manuscript, Approval for publication.

**Melinda A. Pruis:** Conceptualization, Data curation, Formal analysis, Investigation (body composition analysis), Methodology, Data interpretation, Critical reviewing of the manuscript, Approval for publication.

**Barend J. Sikkema:** Writing-revisions, Data interpretation, Critical reviewing of the manuscript, Approval for publication.

**Mostafa Mohseni:** Conceptualization, Methodology, Investigation (in-depth analysis), Data interpretation, Critical reviewing of the manuscript, Approval for publication.

**G. D. Marijn Veerman:** Formal analysis (pharmacokinetic sampling), Investigation (pharmacokinetic sampling), Data interpretation, Critical reviewing of the manuscript, Approval for publication.

**Marthe S. Paats:** Conceptualization, Methodology, Data interpretation, Critical reviewing of the manuscript, Approval for publication.

**Daphne W. Dumoulin:** Data interpretation, Critical reviewing of the manuscript, Approval for publication.

**Egbert F. Smit:** Data interpretation, Critical reviewing of the manuscript, Approval for publication.

**Annemie M. W. J. Schols:** Conceptualization, Methodology, Data interpretation, Critical reviewing of the manuscript, Approval for publication.

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**Elisabeth F.C. van Rossum:** Conceptualization, Methodology, Investigation (in-depth analysis), Data interpretation, Critical reviewing of the manuscript, Approval for publication.

**Anne-Marie C. Dingemans:** Conceptualization, Methodology, Supervision, Data interpretation, Critical reviewing of the manuscript, Approval for publication.

All authors were involved in the data interpretation, critically reviewed the data and manuscript, and gave final approval for publication.

## Ethics Approval

The START-TKI trial is approved by the local ethics committee (Erasmus University Medical Center Rotterdam; MEC 2019-0654) and was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT05221372).

## Consent to Participate

All participating patients gave written informed consent.

## Data Availability

The data sets generated during and/or analyzed during this trial are available through the corresponding author on reasonable request.

## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at [www.jto.org](http://www.jto.org) and at <https://doi.org/10.1016/j.jtho.2023.03.020>.

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