ORIGINAL ARTICLE

Meta-Analysis Exploring Tyrosine Kinase Inhibitor-Induced Weight Gain in Oncogene-Addicted NSCLC

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ABSTRACT

Background: For patients with oncogene-addicted NSCLC treated with tyrosine kinase inhibitors (TKIs), weight gain has recently gained attention as a frequent treatment-related effect. Identifying those TKIs more frequently associated with weight gain is crucial for further characterizing body composition-related modifications, deepening their metabolic impact, and guiding treatment decisions, considering the potential influence of weight gain on patients' quality of life and long-term outcomes.

Methods: A systematic search was conducted across PubMed, Scopus, Cochrane, and meeting resources. A meta-analysis was conducted to quantify the magnitude of weight gain, and meta-regression was applied to explore the association between this side effect, and demographic and clinical parameters.

Results: Among 7596 identified studies from January 2009 to December 2024, 18 pivotal trials reporting weight gain data were included in the final analysis, encompassing a total of 25 arms. Lorlatinib revealed the highest risk of treatment-induced weight gain [incidence 36%; 95% confidence interval (CI): 26%–46%; $I^2 = 92\%$], followed by alectinib [incidence 15%; 95% CI: 12%–18%; $I^2 = 52\%$] and crizotinib [incidence 5%; 95% CI: 0%–13%; $I^2 = 93\%$]. Osimertinib and erlotinib indicated the lowest incidence of weight gain. The meta-regression revealed no significant correlation among weight gain, sex, age, and performance status, thus suggesting a drug-specific effect.

Conclusions: Our findings confirmed the unique profile of lorlatinib regarding weight gain, regardless of patient characteristics. Considering the impressive prognostic horizons achievable with TKIs in oncogene-addicted NSCLC, adequate reporting in clinical trials, assessment and monitoring of weight gain, body composition modifications, and impact on quality of life should be prioritized, together with adequate lifestyle-based strategies for its management.

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Keywords: NSCLC; Oncogene-addicted; TKIs; Weight gain

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Introduction

Treatment strategies for oncogene-addicted (OA) NSCLC are continuously evolving in terms of type, number of options (more druggable alterations and more drugs for each target) and expected efficacy. In the era of targeted therapy, tyrosine kinase inhibitors (TKIs) in particular radically prolonged the patients' prognosis, markedly increasing survival rates and improving disease-related outcomes. TKIs are now available against at least nine different genes (encompassing several molecular alterations), either as first-line or subsequent-line treatments, with many ongoing clinical trials evaluating novel molecules and combination approaches.[1] These agents generally exhibit favorable safety profiles, with most patients experiencing only mild-to-moderate adverse effects. Grade 3 or higher toxicities are relatively uncommon.[2–4] Nevertheless, distinct and previously not very worrisome side effects, different from those typically associated with cancer treatments, are increasingly being reported and recently highlighted, presenting patients and clinicians with unique challenges. Among these, weight gain has recently garnered increasing attention as a clinically relevant treatment-related effect in patients with OA NSCLC, particularly associated with the use of newer-generation TKIs.[5] Although often overlooked, this side effect can profoundly affect patients' quality of life (QoL) and warrants further investigation in terms of metabolic and clinical implications. Identifying those TKIs more frequently associated with weight gain is essential to plan a detailed evaluation of this phenomenon, providing essential insights into the underlying mechanisms driving consequent changes in body composition, such as alterations in fat distribution, muscle mass, and fluid retention. Understanding these mechanisms is crucial not only for predicting which patients may be more susceptible to weight gain but also for implementing targeted (pharmacological and/or non-pharmacological) strategies to mitigate its impact and consequences. This meta-analysis aims to enhance the characterization of TKI-associated weight gain, thereby facilitating a more accurate assessment of its clinical relevance and supporting clinicians in making more informed treatment decisions, ultimately enhancing patient care and preserving QoL.

Materials and Methods

The present review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[6] and the protocol registered on the International Prospective Register of Systematic Reviews (CRD42024564655).

Search Strategy

From inception to May 2024 and subsequently updated in January 2025, a systematic search was conducted across the electronic databases PubMed, Scopus, and Cochrane, and conference proceedings of the American Society of Clinical Oncology and European Society of Medical Oncology congresses. The Supplementary Materials reported the full search strategy, predominantly based on three primary keyword categories, that is, disease-related (e.g., lung cancer), treatment-related (e.g., TKI), and outcome-related (e.g., weight gain). After removing duplicates, screening for title and abstract was performed by two independent authors (IMS and SE). If the abstract did not report sufficient information, the studies were selected for full-text evaluation. At least two independent authors (IMS, AA, SE, and AB) evaluated the full-text articles, and disagreements were resolved through consensus with a third investigator (LB). In addition, the reference lists of included studies were manually reviewed to identify any relevant articles.

Eligibility Criteria

Studies were deemed eligible for inclusion if they were (1) randomized controlled trials, single-arm studies, or observational or real-world studies; (2) included adult patients with NSCLC receiving any TKI therapy; and (3) assessed the incidence of weight gain as treatment-related adverse events. The exclusion criteria were (1) non-English language publications, (2) studies including patients with cancer types other than lung cancer, (3) studies assessing TKIs in combination with other anticancer treatments, and (4) weight gain not reported as outcomes.

Data Extraction and Quality Assessment

Data were extracted and summarized in an Excel spreadsheet (Microsoft, Redmond, WA) by two independent researchers (IMS and SE), and LB resolved disagreements. The following variables were collected: study information (authors, study design, country, sample size), patient demographic and medical characteristics (type of lung cancer, stage, molecular profile, type and scheme of TKI, prior treatments, presence of comorbidities, mean age, sex, and performance status), and outcome measures [number and percentage of patients who overall experienced weight gain as adverse events (AEs), the grade of AEs, classified as mild (grade 1–2) and severe (grade 3–5), and methods of evaluation of weight gain]. If studies reported only the incidence of grade 3 or greater of AEs, the remaining were deemed grade 1 to 2.

Study Quality Assessment

The quality of interventional studies was assessed with the Cochrane Risk of Bias 2.0 and Risk Of Bias In Nonrandomized Studies—of Interventions tools for randomized and nonrandomized trials, respectively, and categorized as "high risk," "some concerns," or "low risk of bias." Studies with a final score of fewer than 5 points are deemed to have a "high risk of bias."

Statistical Analysis

The incidence of overall weight gain was logit transformed and pooled using the inverse sampling variance method. The pooled estimate for the incidence rate was measured using random-effects or fixed-effects models, depending on the heterogeneity of the studies. Statistical heterogeneity was assessed using Cochran's Q-test, and the inconsistency was quantified with the I^2 statistic. Publication bias was explored with the funnel plots and Egger's test. In addition, a meta-regression was performed to quantify the association of age, sex, and performance status with weight gain. Meta XL for Microsoft Excel and IBM SPSS v.28.0 were used for the analysis.

Results

Study Selection

A total of 7596 studies were identified from our search, with 6996 potential records assessed for title and abstract after duplicate removals. After excluding 6676 records owing to their irrelevance in this meta-analysis, 320 were deemed eligible for full-text evaluation. Overall, 300 were excluded owing to the lack of weight gain data and two for other reasons (Supplementary Table 1), leaving 18 studies that met the inclusion criteria and have been included in the final analysis (Fig. 1).

Study and Sample Characteristics

Table 1[7–24] lists the study characteristics. One study was an observational retrospective analysis, six single-arm trials, three pooled analyses, and eight randomized trials. Among the randomized trials, one was a pooled analysis, and seven comprised a three-arm trial, including two treatment arms with TKIs, leading to separate evaluations for each arm and overall considering 25 treatment arms in the analysis. Two studies evaluated erlotinib and osimertinib, respectively;[15,20]

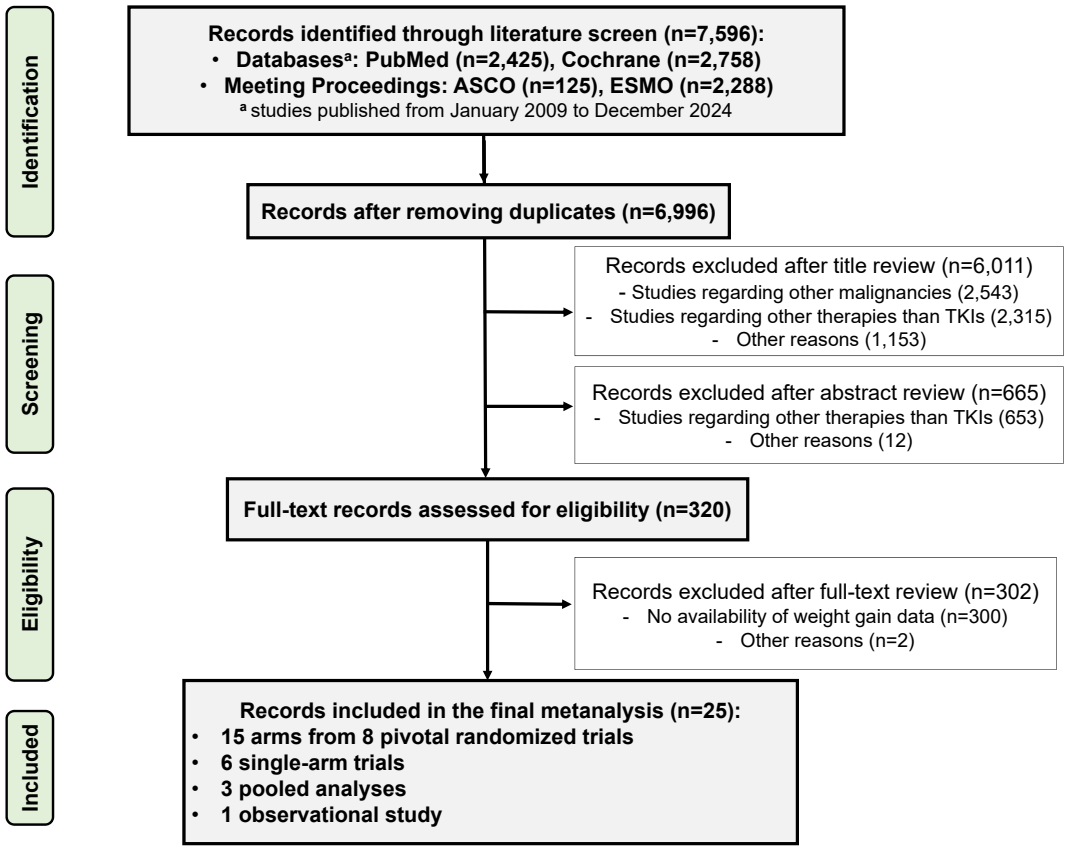

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the included studies. ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; TKI, tyrosine kinase inhibitors.

Table 1. Characteristics of the Studies Included in the Meta-Analysis

Study	Study Design (Phase)	Histologic Diagnosis	Molecular Profile	Stage	Drug	Patients (N)	Age (y)	Men (n)	ECOG PS ≥2 (n)	Never-Smoker (n)	Brain Metastases (n)	Asian/non-Asian pts (n)
Peters et al.[7]	Randomized (phase 3)	NSCLC (adenocarcinoma, large-cell carcinoma, squamous-cell carcinoma, undifferentiated	ALK rearrangement	IIIB-IV	Alectinib Crizotinib	151 152	58 54	68 64	10 10	92 98	64 58	69/83 69/82
Shaw et al.[8]	Single-arm (phase 1)	NSCLC	ALK or ROS1 rearrangement	IIIB-IV	Lorlatinib	54	50	22	2	NA	39	7/47
Yang et al.[9]	Pooled analysis (phase 2)	NSCLC, adenocarcinoma, other not specified	ALK rearrangement	IV	Alectinib	225	53	100	22	150	136	43/186
Solomon et al.[10]	Single-arm (phase 2)	NSCLC	ALK or ROS1 rearrangement	IV	Lorlatinib	275	54	118	10	NA	166	103/172
Shaw et al.[11]	Single-arm (phase 1/2)	NSCLC	ROS1 rearrangement	IV	Lorlatinib	69	54	30	2	NA	39	22/47
Zhou et al.[12]	Randomized (phase 3)	NSCLC, adenocarcinoma, other not specified	ALK rearrangement	IIIB-IV	Alectinib Crizotinib	125 62	51 49	64 34	4 1	84 45	44 23	125/0 62/0
Camidge et al.[13]	Randomized (phase 3)	Adenocarcinoma, large-cell carcinoma, mixed, squamous-cell, undifferentiated, other	ALK rearrangement	IIIB-IV	Alectinib Crizotinib	152 151	58 54	68 64	10 10	92 98	64 58	69/83 69/82
Shaw et al.[14]	Randomized (phase 3)	Adenocarcinoma, adenosquamous carcinoma, large-cell carcinoma, squamous-cell carcinoma	ALK rearrangement	IIIA-IV	Lorlatinib Crizotinib	149 142	61 56	65 56	3 9	81 94	38 40	65/84 65/82
Wu et al.[15]	Randomized (phase 3)	Nonsquamous, adenocarcinoma, other	EGFR: Ex19del, L858R, or T790M	IB-IIIA	Osimertinib	337	64	108	0	68	0	64/36
Ou et al.[16]	Pooled analysis (phase 2)	Adenocarcinoma, squamous cell carcinoma, adenosquamous, large cell carcinoma	ALK rearrangement	IIIB-IV	Alectinib	225	53	100	22	NA	136	43/182
Felip et al.[17]	Single-arm (phase 2)	Adenocarcinoma	ALK or ROS1 rearrangement	IV	Lorlatinib	278	54.3	122	12	NA	190	106/172

(continued)

Table 1. Continued

Study	Study Design (Phase)	Histologic Diagnosis	Molecular Profile	Stage	Drug	Patients (N)	Age (y)	Men (n)	ECOG PS ≥2 (n)	Never-Smoker (n)	Brain Metastases (n)	Asian/non-Asian pts (n)
Lu et al.[18]	Single-arm (phase 2)	NSCLC	ALK rearrangement	IV	Lorlatinib	109	51	53	5	69	NA	109/0
Dagogo-Jack et al.[19]	Single-arm (phase 2)	NSCLC	ALK rearrangement	IV	Lorlatinib	23	58	13	3	18	5	5/18
Piccirillo et al.[20]	Randomized (phase 3)	Adenocarcinoma	EGFR: Ex19del or L858R	IV	Erlotinib	80	67.7	30	4	37	NA	NA
Zhou et al.[21]	Randomized (phase 3)	NSCLC	ALK rearrangement	IIIA-IV	Lorlatinib Crizotinib	59 60	61 60	13 10	1 2	NA NA	11 15	50/0 61/0
Solomon et al.[22]	Randomized (phase 3)	Adenocarcinoma, adenosquamous carcinoma, large-cell carcinoma, squamous-cell carcinoma	ALK rearrangement	IIIA-IV	Lorlatinib Crizotinib	149 142	61 56	65 56	3 9	81 94	38 40	65/84 65/82
John et al.[23]	Observational retrospective	NSCLC	ALK or ROS1 rearrangement	IV	Lorlatinib	43	55.5	18	NA	NA	NA	NA
Sikkema et al.[24]	Pooled analysis (phase 3)	NSCLC	ALK rearrangement	IIIB-IV	Alectinib Alectinib	103 199	NA NA	41 97	2 17	56 119	14 143	NA 20/179

ECOG PS, Eastern Cooperative Oncology Group Performance Status; NA, not available; pts, patients.

six assessed crizotinib,[7,12–14,21,22] seven alectinib,[7,9,12,13,16,24] and ten lorlatinib.[8,10,11,14,17–19,21–23]

Overall, 3514 patients were included in the studies; the median age was 55 years; 43.03% were men; 4.92% indicated Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 2 or greater; 39.17% were never-smokers, and 37.60% had brain metastases at baseline. According to treatment options, 1208 patients received lorlatinib (54.5 years median age; 44.54% men; 3.4% ECOG PS ≥2; 20.61% never-smokers; 43.54% brain metastases), 1180 with alectinib (55.0 years median age; 45.59% men; 7.37% ECOG PS ≥2; 50.25% never-smokers; 50.93% brain metastases), 709 with crizotinib (54.5 years median age; 42.03% men; 5.78% ECOG PS ≥2; 60.49% never-smokers; 32.99% brain metastases), 337 with osimertinib (64.0 years median age; 32% men; 0% ECOG PS ≥2; 20.06% never-smokers; 0% brain metastases), and 80 were treated with erlotinib (67.7 years median age; 37.5% men; 5% ECOG PS ≥2; 46.25% never-smokers; not available brain metastases).

The study quality assessment is summarized in the Supplementary Materials (Supplementary Figs. 1 and 2). Among the single-arm studies, six reported a moderate risk of bias. Regarding the randomized trials, the bias was deemed low in all five. The observational study was classified as moderate quality.

The Rate of Weight Gain

Table 2 reports information regarding the assessment and incidence of weight gain. Weight gain was evaluated according to the Common Terminology Criteria for Adverse Events versions 4.0 and 5.0 in most of the included studies[7–14,16–19,21–23] In these cases, weight gain was defined as an unexpected or abnormal increase in overall body weight from baseline. It was categorized into three severity grades: grade 1 (5% to <10% increase), grade 2 (10% to <20% increase), and grade 3 (≥20% increase). In the pooled analysis, the percentage of patients experiencing weight gain was reported without further details regarding the extent and severity of the weight changes.[16,24]

Overall, a mean of 19% of patients experienced weight gain as an AE during TKI treatment. In 14% of patients, weight gain was classified as mild (grade 1–2), and in 7% as severe (grade 3). In the meta-analysis, the

Table 2. Incidence of Weight Gain in Patients Receiving Tyrosine Kinase Inhibitors, According to the Severity

Study	Drug	No. of pts weight gain, any grade (%)	Grade 1-2 n (%)	Grade 3 n (%)
Peters et al.[7]	Alectinib	15 (10)	14 (9)	1 (1)
Peters et al.[7]	Crizotinib	0 (0)	0 (0)	0 (0)
Shaw et al.[8]	Lorlatinib	9 (17)	6 (11)	3 (6)
Yang et al.[9]	Alectinib	33 (15)	NA	NA
Solomon et al.[10]	Lorlatinib	50 (18)	45 (16)	5 (2)
Shaw et al.[11]	Lorlatinib	16 (23)	11 (16)	5 (7)
Zhou et al.[12]	Alectinib	23 (18)	19 (15)	4 (3)
Zhou et al.[12]	Crizotinib	2 (3)	1 (1)	1 (2)
Camidge et al.[13]	Alectinib	14 (9)	NA	NA
Camidge et al.[13]	Crizotinib	0 (0)	0 (0)	0 (0)
Shaw et al.[14]	Lorlatinib	57 (38)	28 (21)	25 (17)
Shaw et al.[14]	Crizotinib	18 (13)	15 (10)	3 (2)
Wu et al.[15]	Osimertinib	0 (0)	0 (0)	0 (0)
Ou et al.[16]	Alectinib	19 (16)	15 (7)	4 (9)
Felip et al.[17]	Lorlatinib	70 (24)	55 (19)	15 (5)
Lu et al.[18]	Lorlatinib	35 (32)	28 (26)	7 (6)
Dagogo-Jack et al.[19]	Lorlatinib	9 (39)	8 (35)	1 (4)
Piccirillo et al.[20]	Erlotinib	1 (1)	0 (0)	1 (1)
Zhou et al.[21]	Lorlatinib	29 (49)	19 (32)	10 (17)
Zhou et al.[21]	Crizotinib	10 (17)	9 (15)	1 (2)
Sikkema et al.[24]	Alectinib	23 (22)	NA	NA
Sikkema et al.[24]	Alectinib	15 (16)	NA	NA
Solomon et al.[22]	Lorlatinib	66 (44)	32 (21)	34 (23)
Solomon et al.[22]	Crizotinib	18 (13)	15 (11)	3 (2)
John et al.[23]	Lorlatinib	35 (81)[a]	15 (35)	4 (9)

Weight gain was evaluated according to the Common Terminology Criteria for Adverse Events versions 4.0 and 5.0.2.
[a]Weight gain <grade 1 was reported in 37.2% of the pts.
NA, not available; pts, patients.

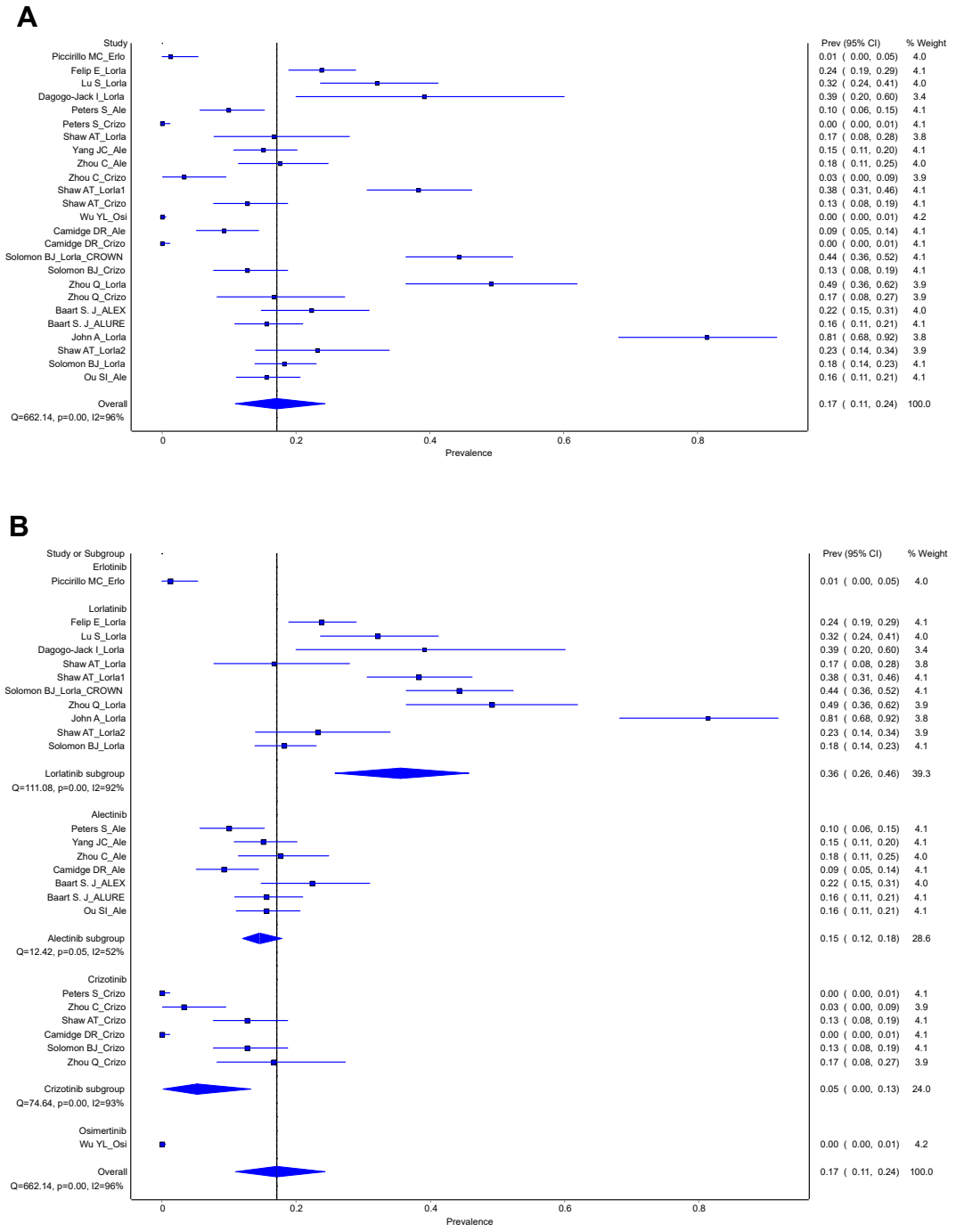

Figure 2. *(A)* Forest plot of results of a meta-analysis evaluating percentage of patients with weight gain. Each square represents the hazard ratio for weight gain in individual studies. The horizontal line through each square indicates the 95% CI for the hazard ratio, reflecting the range of uncertainty around the estimate of effect. The diamonds represent the estimated overall effect based on the meta-analysis random effects of the trials. *(B)* Forest plot of analysis stratified by subgroups of tyrosine kinase inhibitors. CI, confidence interval.

pooled overall incidence of weight gain was 17% (95% confidence interval [CI]: 11%–24%) (Fig. 2*A*). The heterogeneity was 96%, probably owing to large divergences across the studies and types of treatment.

To further investigate this finding, a subgroup analysis was conducted according to treatment type (Fig. 2*B*). The lorlatinib subgroup reported the highest percentage of weight gain, with a mean of 33% patients experiencing this AE (23% grade 1–2; 10% grade 3); the pooled estimate reported an overall incidence of 36% of weight gain (95% CI: 26%–46%; $I^2 = 92\%$). Across the seven arms assessing alectinib, weight gain

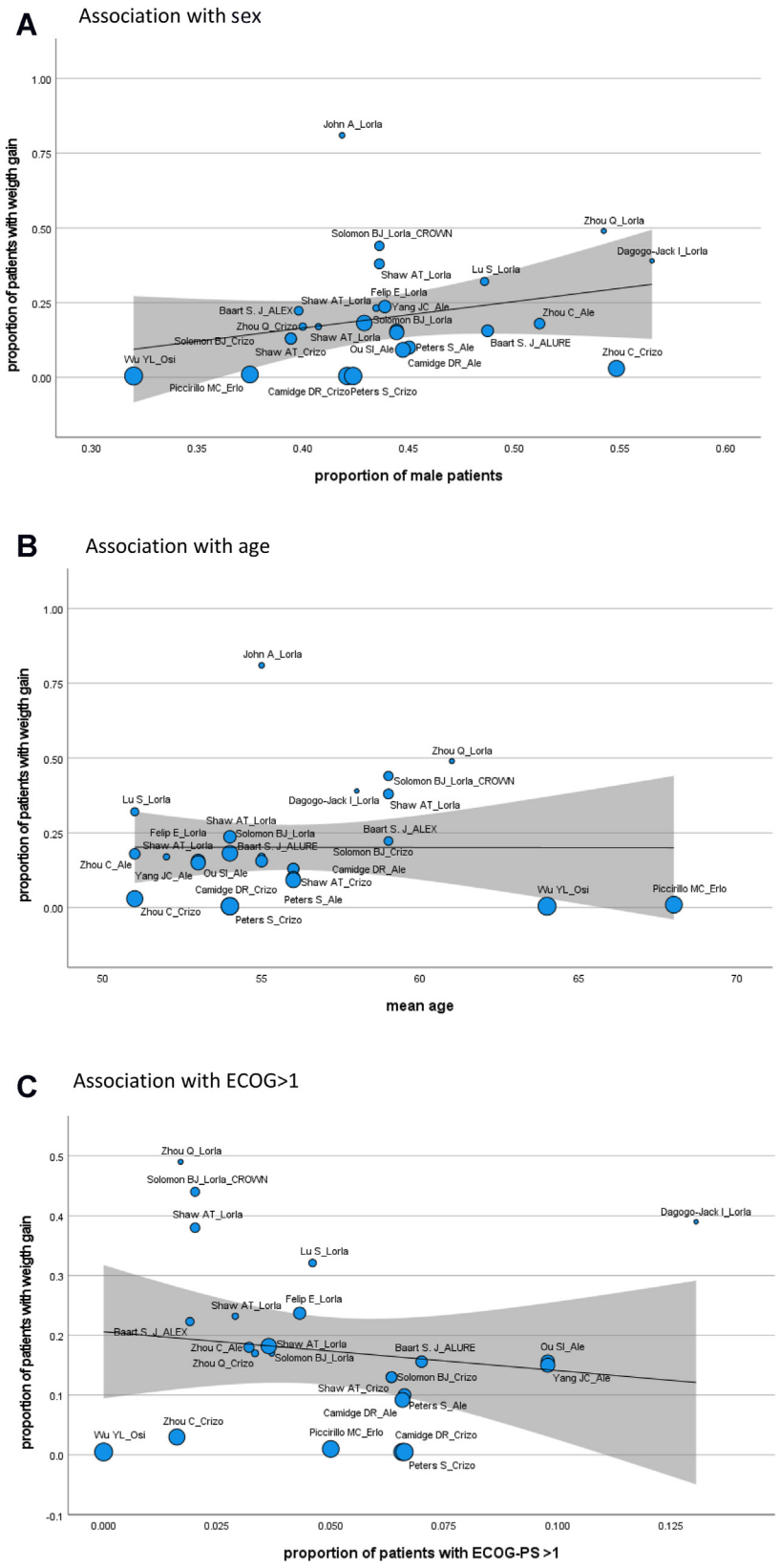

Figure 3. Meta-regression analysis exploring the association between weight gain and sex *(A)*, age *(B)*, and ECOG PS *(C)*. *(A)* No association with sex ($p = 0.19$); $\beta = 0.886$ (S.E. 0.650) (95% CI: -0.46 to $+2.23$). *(B)* No association with age ($p = 0.99$); $\beta = -0.0001$ (SE 0.009) (95% CI: -0.02 to $+0.02$). *(C)* No association with ECOG>1 ($p = 0.50$); $\beta = -0.651$ (SE 0.949) (95% CI: -2.62 to $+1.32$). CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

occurred in a mean of 15% of patients (10% grade 1–2; 4% grade 3); the fixed-effect model revealed an incidence rate of 15% (95% CI: 12%–18%; I^2 = 52%). A mean of 8% of patients (6% grade 1–2; 1% grade 3) experienced weight gain during crizotinib treatment; the pooling of the studies found the overall incidence of such an AE was 5% (95% CI: 0%_13%; I^2 = 93%). The two studies assessing osimertinib and erlotinib reported an incidence of 0% (95% CI: 0%–1%) and 1% (95% CI: 1%–5%), respectively, of weight gain. Funnel plots and Egger's test are presented in the Supplementary Materials (Supplementary Fig. 3).

The meta-regression revealed that age ($\beta = -0.0001 \pm 0.009$; $p = 0.99$), sex ($\beta = 0.866 \pm 0.650$; $p = 0.18$), and performance status ($\beta = -0.651 \pm 0.949$; $p = 0.50$) were not significantly associated with AE, suggesting that weight gain was not primarily driven by individual patient characteristics but rather by the specific TKI used in treatment (Fig. 3).

Discussion

The broad implementation of new TKIs in the lung cancer treatment scenario led to outstanding prognostic horizons but poses novel challenges in facing frequent, potentially long-term, and hard-to-manage AEs with relevant impact on patients' QoL. Although increasing attention has been dedicated to other clinically relevant toxicities such as neurocognitive AEs,[25] weight gain remains a relatively unexplored area of investigation in terms of assessment, reporting, underlying mechanisms, potential implications, and effective management.

Our meta-analysis systematically assessed the incidence of weight gain among patients with OA NSCLC treated with any TKIs. As previously revealed, among the TKIs analyzed and with this AE reported from clinical trials, patients treated with lorlatinib reported the highest incidence of weight gain, with a prevalence of 36%, followed by alectinib (15%) and crizotinib (5%) (Fig. 4). This finding identifies weight gain as one of the most frequent AEs occurring with lorlatinib,

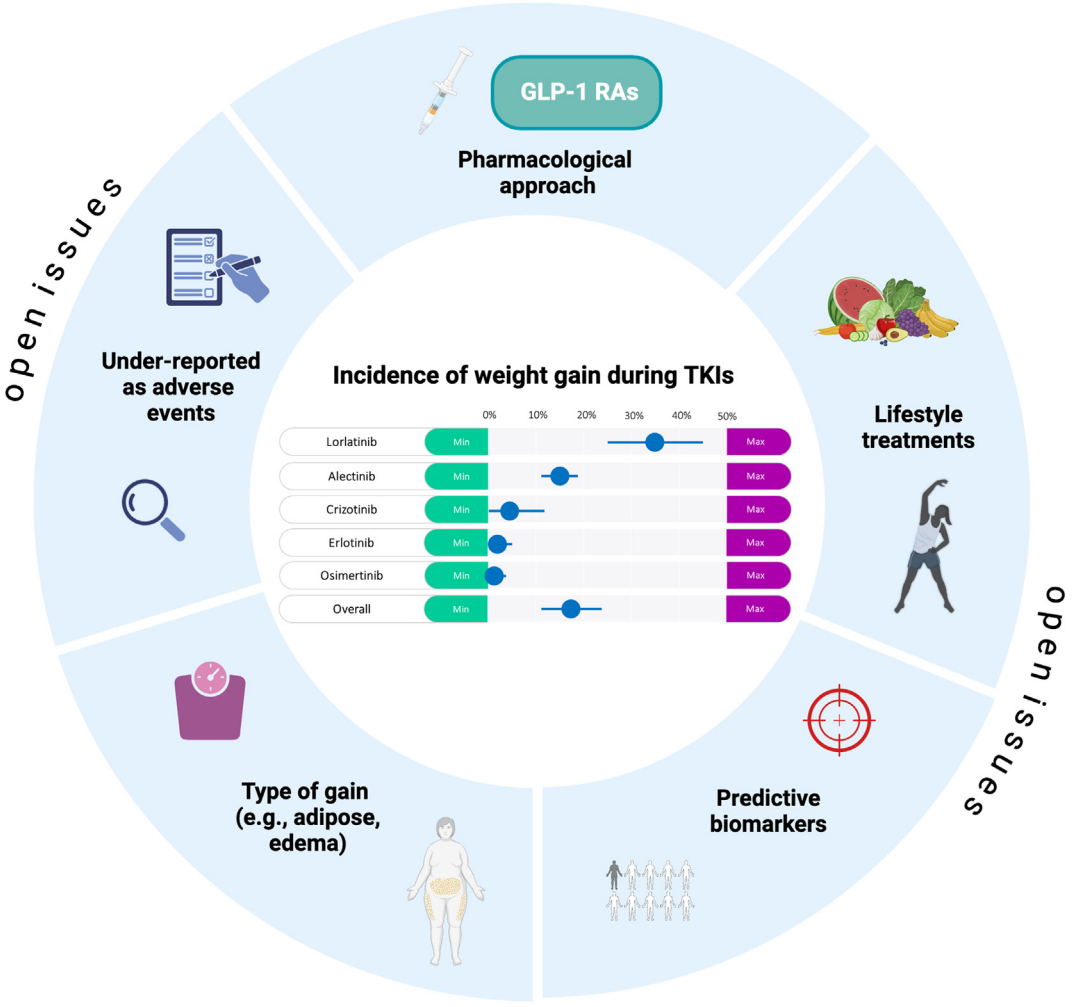

Figure 4. Meta-analysis primary results and open issues. GLP, glucagon-like peptide-1 receptor agonists.

requiring oncologists' awareness and interest. In the CROWN (lorlatinib versus crizotinib in patients with advanced *ALK*-positive NSCLC) trial, 44% of patients treated with lorlatinib experienced weight gain, being grade 3 in 20% of patients.[14,25] The incidence and prevalence of weight gain tend to increase over time, with a median time to onset of 112 days and a median duration of 778 days, highlighting that weight gain represents a long-lasting or chronic toxicity.[25,26] Dose modifications for weight gain alone are only recommended if weight continues to be severely bothersome after the addition of lifestyle modifications.[25]

Deepening features of TKIs-induced weight gain in a prospective cohort of 46 patients treated with alectinib, De Leeuw et al. observed a considerable increase in waist circumference and in visceral and subcutaneous adipose tissue after 3 months, and after 1 year after treatment initiation.[27] This modulation toward an increase in adipose tissue was subsequently associated with a relevant 40% increase in the incidence of abdominal obesity and sarcopenic obesity.[27] This condition could be particularly alarming, given sarcopenic obesity is a recognized prognostic factor, and a risk factor for several chronic conditions, including cardiovascular and metabolic diseases. Although weight gain associated with TKIs (especially ALK inhibitors) could be related to an increase in appetite and consequently in daily caloric intake in patients who are usually physically inactive,[25,28] to date, the underlying mechanisms are not completely elucidated, and future studies should explore both patient- and treatment-related factors. The occurrence of edema, both central and peripheral, could contribute to weight gain during ALK-TKIs, considering that these AEs are often concurrently experienced.[29] Peripheral edema associated with crizotinib is related to c-MET inhibition, such as that observed with MET-TKIs.[30] In contrast, the pathophysiology of edema in patients treated with other ALK inhibitors is not completely elucidated.[31,32] In the ALEX (alectinib versus crizotinib in treatment-naive advanced *ALK*-positive NSCLC) trial, peripheral edema was reported in 31.8% of patients treated with crizotinib and 18.4% of those treated with alectinib.[13] Edema was also reported in 56% of patients treated with lorlatinib in the CROWN study.[29] Lorlatinib-associated edema is most frequently reported as peripheral edema or swelling, although facial and periorbital edema have also been reported.[28] Interestingly, the mechanisms underlying lorlatinib-associated weight gain may involve metabolic alterations such as adipose tissue redistribution and fluid retention, potentially related to ALK inhibition.[31] This AE occurs with a median time to onset of 42 days and a median duration of 163 days, and it is the most common reason for dose reduction (7%).[25,29] In this context, adequate management of edema should be prioritized to favor also weight loss, and in this sense, a lifestyle-based intervention may contribute to control both toxicities.[25]

Another important observation emerging from this study is related to the probability that weight gain could have been frequently under-reported in pivotal clinical trials. During the screening phase for this meta-analysis, although weight loss was assessed in most of the studies, weight gain began to be reported as an AE only after 2017, and among 320 studies, only 18 reported weight gain as an AE (Fig. 1). Weight gain was first included in Common Terminology Criteria for Adverse Events version 3.0 in 2006.[33] From one perspective, this may reflect the perception of disease-related weight modifications because historically, weight loss was deemed more alarming than weight gain. This could also be related to the amount of evidence that highlights ways sarcopenia, that is, the loss of muscle mass and strength, negatively affects treatment outcomes and survival,[34,35] particularly in the context of immunotherapy.[36–38] In this light, body composition phenotypes may affect the immunologic landscape and thereby modulate antitumor immune response.[39] In contrast, weight gain started to be reported as an AE with the wider introduction of TKIs, for which it was recognized as a potential treatment-related toxicity (Fig. 4). In this perspective, lack of data before 2017 does not definitively exclude the possibility that older TKIs may also lead to this AE. To reinforce this assumption, a pooled analysis of four prospective clinical trials with alectinib found that weight gain was under-reported as an AE in three of those, suggesting that it was often neglected in routine clinical practice.[24] In this sense, the assessment and monitoring (including long-term follow-up) of weight changes in both the clinical trials and the real-world setting could be the first step toward an increased knowledge of its real incidence and potential consequences on patient- and treatment-related outcomes. Nevertheless, the ideal point of arrival to appropriately explore this phenomenon is the implementation of body composition evaluation.

Among the possible strategies for managing weight gain induced by TKIs and more generally, to shape patients' body composition, lifestyle modifications are fundamental (Fig. 4). Physical exercise and nutritional interventions have been found to be safe and feasible approaches in patients with lung cancer, enabling them to increase muscle mass while also modulating adipose tissue.[40] In addition, observational data suggest a correlation between exercise and nutrition, and survival in lung cancer.[41] To our knowledge, no studies have investigated the impact of this combined lifestyle-based approach in managing weight gain induced by TKIs. Nevertheless, given their synergistic effect on determining the daily energy balance, exercise and nutrition

could be important interventions to be explored and proposed in patients at high risk of developing or who have experienced weight gain as a side effect of TKIs.

Interestingly, the integration of a pharmacologic approach to managing TKIs-induced weight gain was recently proposed as an intriguing strategy (Fig. 4). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide, which mimic endogenous GLP-1 activity, have indicated efficacy in achieving clinically relevant weight control.[42] Nevertheless, these trials did not include patients with cancer. To date, only one case report has documented the effectiveness of GLP-1 RAs in addressing alectinib-induced weight gain.[43] Despite this potentiality, concerns remain regarding their common gastrointestinal side effects. Moreover, the first study combining semaglutide with alectinib revealed a clinically relevant 32% reduction in total alectinib exposure compared with alectinib monotherapy after just a single administration of semaglutide, potentially influencing the overall efficacy of the TKIs.[44] Overall, the current lack of robust evidence requires caution in interpreting the safety of combining GLP-1 agonists with TKIs (e.g., potential drug interactions). Given these considerations, further studies evaluating both the efficacy and safety of GLP-1 RAs for managing TKI-induced weight gain are essential before this potentially promising treatment approach may be implemented. In this sense, and to try to save the patient from taking other drugs (with potential interactions and side effects), the lifestyle-based approach may represent the first-line option for managing TKI-induced weight gain in patients with lung cancer, reserving the introduction of a pharmacologic strategy (if found to be effective) as a further option for refractory cases.

The present meta-analysis has some limitations, primarily related to the heterogeneity in study design of the included investigations, the scarce number of trials reporting weight gain, and the absence of information on any concomitant medical conditions or treatments that might influence weight gain (e.g., edema or steroid therapy) and therefore the study results. In addition, our study applied an aggregated meta-analysis approach, considering weight as a singular AE, therefore limiting the possibility of tracking weight change over time. Of note, non-English language studies were excluded, which may have introduced a potential language bias. Furthermore, in the studies included in the meta-analysis, ECOG PS was assessed only at baseline, potentially overlooking improvements during treatment that may have affected appetite, caloric intake, and subsequent weight gain. This may have contributed to the lack of significant association between ECOG PS and weight gain observed in the meta-regression analysis.

Nevertheless, to our knowledge, this meta-analysis is the largest and most comprehensive study evaluating weight gain in patients with NSCLC treated with TKIs, allowing several considerations for future studies and related research. In this light, exploring weight changes occurring with different TKIs, evaluating in depth the modulation of body composition, and dissecting the potential mechanisms of action are of paramount importance. Following this direction, we have designed and are currently conducting a prospective study to assess baseline and longitudinal body composition profiles in patients with NSCLC who undergo TKIs and to test the contribution of patients' lifestyle modifications to these changes, potentially offering novel insights into the prevention and management of this clinically influencing AE.

Conclusions

Our findings confirmed the unique profile of lorlatinib regarding weight gain, independently of patients' demographics or baseline performance status. Considering the impressive prognostic horizons achievable with TKIs in OA NSCLC, adequate reporting in clinical trials, and assessment and monitoring of weight gain, body composition modifications, and impact on QoL should be prioritized, together with adequate lifestyle-based strategies for its management.

CRediT Authorship Contribution Statement

Ilaria Mariangela Scaglione: Conceptualization, Methodology, Writing - original draft preparation.

Alice Avancini: Conceptualization, Methodology, Writing - original draft preparation.

Serena Eccher: Data curation, Writing - original draft preparation.

Anita Borsati: Data curation, Writing - original draft preparation.

Luca Pasqualin: Data curation, Writing - original draft preparation.

Giulia La Cava: Data curation, Writing - original draft preparation.

Ilaria Trestini: Data curation, Writing - original draft preparation.

Daniela Tregnago: Data curation, Writing - original draft preparation.

Marco Sposito: Data curation, Writing - original draft preparation.

Jessica Insolda: Data curation, Writing - original draft preparation.

Diana Giannarelli: Conceptualization, Methodology, Data curation, Writing - original draft preparation.

Michele Milella: Supervision, Validation.

Sara Pilotto: Conceptualization, Methodology, Supervision, Writing - original draft preparation, Writing - review and editing.

Lorenzo Belluomini: Conceptualization, Methodology, Supervision, Writing - original draft preparation, Writing - review and editing.

Disclosure

Dr. Pilotto received consulting fees from AstraZeneca, MSD, Eli Lilly, Roche, AMGEN, Pierre-Fabre, Daichii-Sankyo, Pfizer, Boehringer Ingelheim, and Regeneron; payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from AstraZeneca, MSD, Eli Lilly, Roche, AMGEN, Daichii-Sankyo, Boehringer Ingelheim, Johnson & Johnson, and Novartis; and support for attending meetings and/or travel from Roche, Johnson & Johnson, and AMGEN, outside the submitted manuscript. Dr. Belluomini received speakers' fees from AstraZeneca, Merck, Sharp & Dohme, and Roche, outside the submitted manuscript; and travel fees from Takeda. The remaining authors declare no conflict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2025.100881.

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